

RENAL DISEASE IN DIABETES

with special reference
to the
Kimmelstiel Wilson Syndrome.

by

IAN GILLILAND.



CONTENTS.

Chapter 1.	Introduction	Page 1
Chapter 2.	Analysis of the Pathological Material	4
Chapter 3.	Analysis of the Clinical Material	46
Chapter 4.	Ancillary aids to Diagnosis	50
	Repeated Addis Counts	50
	Quantitative measurements of Albuminuria	52
	Doubly Refractile Bodies in the urine	53
Chapter 5.	Dynamic Studies of Renal Function	57
	Method	57
	Clearances of normal Diabetics	66
	Clearances of Kimmelstiel Wilson Syndromes	67
	Clearances of Arteriosclerotic Diabetics	68
	Clearance of Chronic Glomerulonephritis in a Diabetic	69
Chapter 6.	Summary	73
Chapter 7.	References arranged alphabetically	77
Appendix A.	Case Histories of the Pathological Analysis Chapter 2.	
Appendix B.	Case Histories of the Clinical Analysis Chapter 3.	

INTRODUCTION.

Diabetics are particularly liable to develop kidney disease. This is partly due to the fact that some renal conditions occur more frequently and with greater severity in the diabetic. Such are the infective complications, ranging from subclinical pyelitis to necrotising renal papillitis, and the degenerative diseases of the renal arteries and arterioles. But it is also due to one condition, called intercapillary glomerulosclerosis by Kimmelstiel & Wilson (1936) which is almost peculiar to diabetics. Infection can be demonstrated from the urine, and renal arterial disease inferred from the clinical evidence of generalised arterial disease, but there are no accepted clinical criteria for recognising the presence of intercapillary glomerulosclerosis during life.

Several clinical and pathological studies of intercapillary glomerulosclerosis have appeared since the original observations, many tending to confirm that the typical lesions are associated with a recognisable syndrome, but others describing cases in which many of the clinical features were not present. More recently, Kimmelstiel & Porter (1948) have done much to clarify this position by suggesting that two distinct and perhaps different lesions have been recognised in the literature as intercapillary glomerulosclerosis - a "diffuse" and a "nodular"

form. They observe that the evidence of the literature shows that the "nodular" type is, (as Bell (1942) suggested,) a lesion found almost exclusively in diabetics, and that it is most likely to show a clear-cut syndrome. Further, since the original paper of Kimmelstiel & Wilson refers clearly to cases showing the "nodular" form, only such a lesion should be described as the lesion of intercapillary glomerulosclerosis or the Kimmelstiel Wilson lesions. This thesis is based upon this interpretation of the lesion. But still no agreement has been reached about the clinical syndrome which should suggest this lesion. It was therefore decided to investigate this problem on the following lines.

We decided to examine and classify all the available pathological material from diabetic autopsies at Hammersmith Hospital grouping those cases showing Kimmelstiel Wilson lesions separately from those showing other renal pathology. We then made an analysis of the clinical records and compared the clinical syndromes shown by the various groups of renal pathology. From this analysis, and from the experience of others in the literature, we defined the fully developed Kimmelstiel Wilson syndrome.

All the available clinical material in hospital and attending the diabetic clinic was then examined, and cases exhibiting the fully developed syndrome

were then studied, to determine the march of signs and symptoms, and to evaluate several ancillary methods of diagnosis.

Finally comparative studies of renal function in diabetics were made by clearance techniques, comparing the renal dynamics of normal diabetics, with those exhibiting the Kimmelstiel Wilson syndrome, with arteriosclerotic diabetics, and with one case of chronic glomerulo nephritis in a diabetic. The results of these investigations are presented in this thesis.

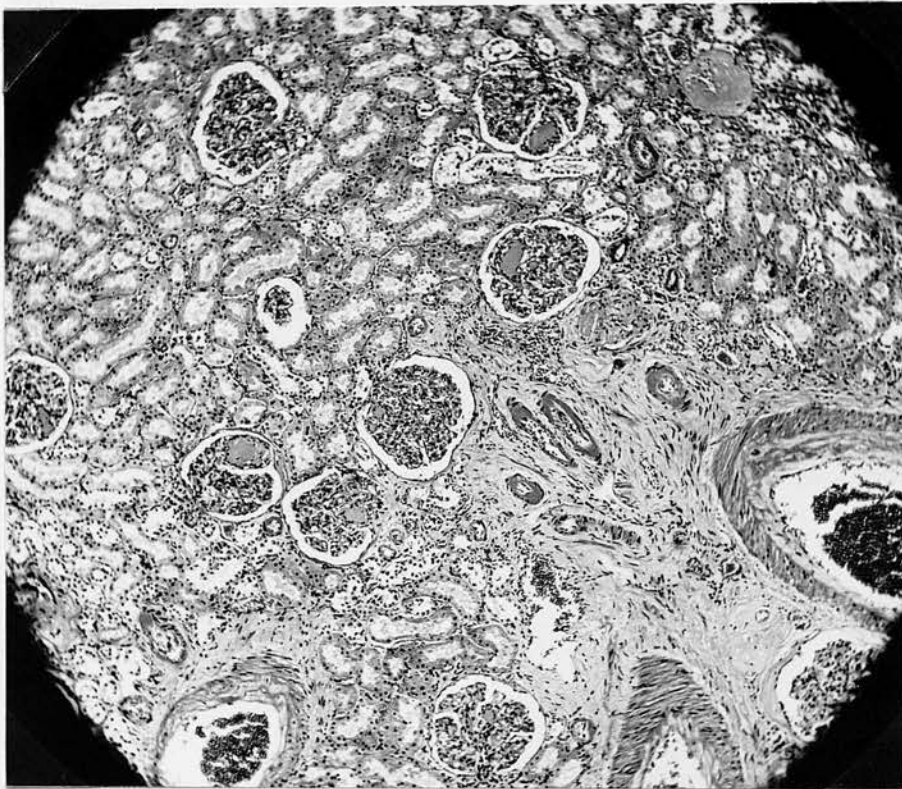
CHAPTER 2.

ANALYSIS OF THE PATHOLOGICAL MATERIAL.

It seemed as though a comparison between the clinical syndrome recorded in association with different types of renal pathology in diabetics should show whether there was a syndrome associated with this lesion, at least in its advanced stages. Such a comparison was then made after analysing the clinical records and post mortem material of all diabetics coming to autopsy in Hammersmith Hospital from July, 1936 to August, 1948. The cases were classified according to their renal pathology into one of the 5 groups shown below, and a comparison between the clinical features of these 5 groups provides the results presented in this chapter.

PATHOLOGICAL GROUPING. There were 46 cases. Three were discarded as adequate pathological material was not available. There were no cases of nephritis. The remaining 43 were placed in the following groups: Group 1. The Kimmelstiel Wilson Group (11 cases, 8 with lesions in nearly every glomerulus, 3 in only occasional glomeruli). All cases showing the nodular intercapillary glomerulosclerosis lesion described by Kimmelstiel & Wilson were placed in this group, irrespective of other pathology; i.e. all cases showed the following features:- (a) discrete

hyaline islands in the glomeruli (Fig.1).



H + E X 60.

A general view showing the discrete nature of the hyaline islands.

The capillaries around them appearing to remain patent and even, in places, dilated (Figs. 2 and 3).

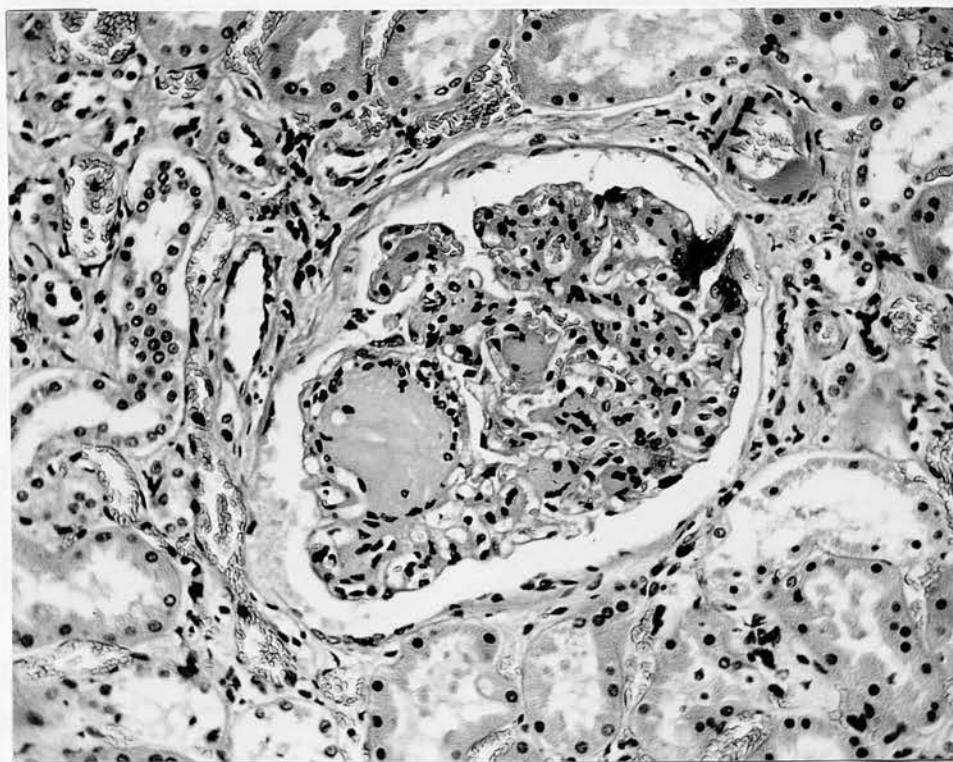


Fig. 2. H + E X 205

Showing that the capillaries remain patent, and even, in places, dilated.

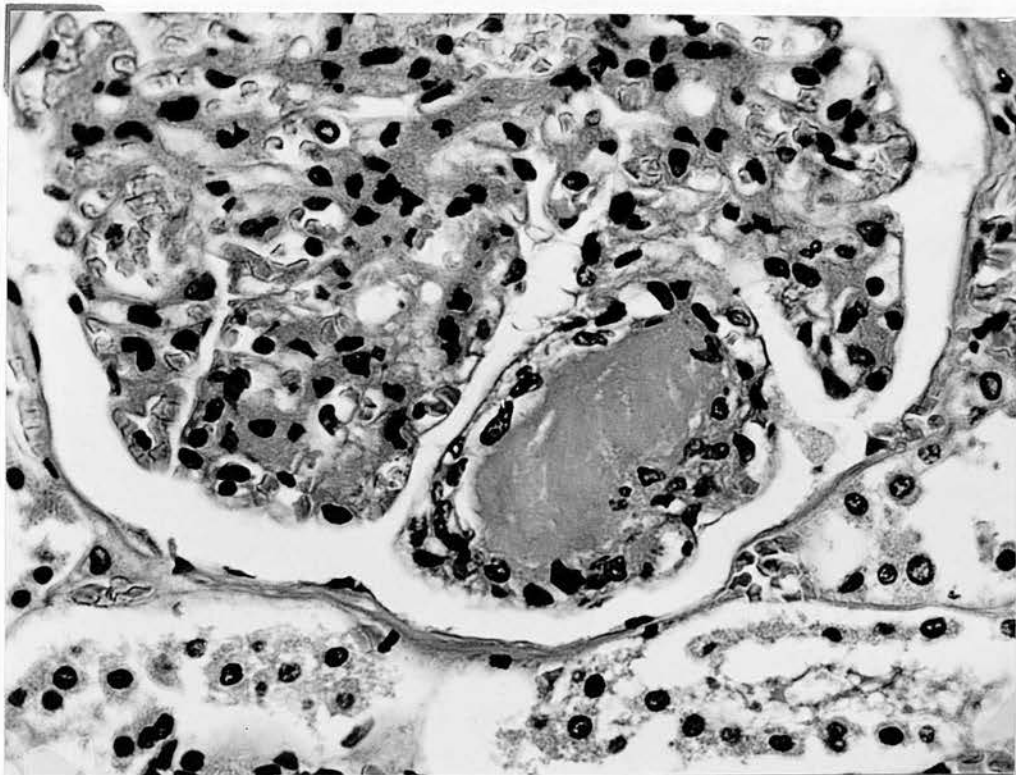
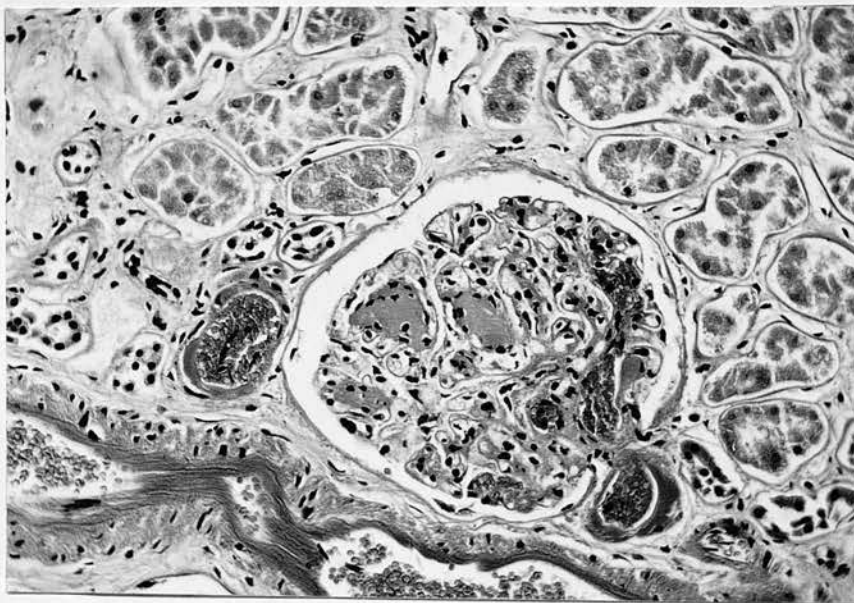


Fig. 3. H + E X 490

A higher power showing the apparent
dilation of the capillaries.

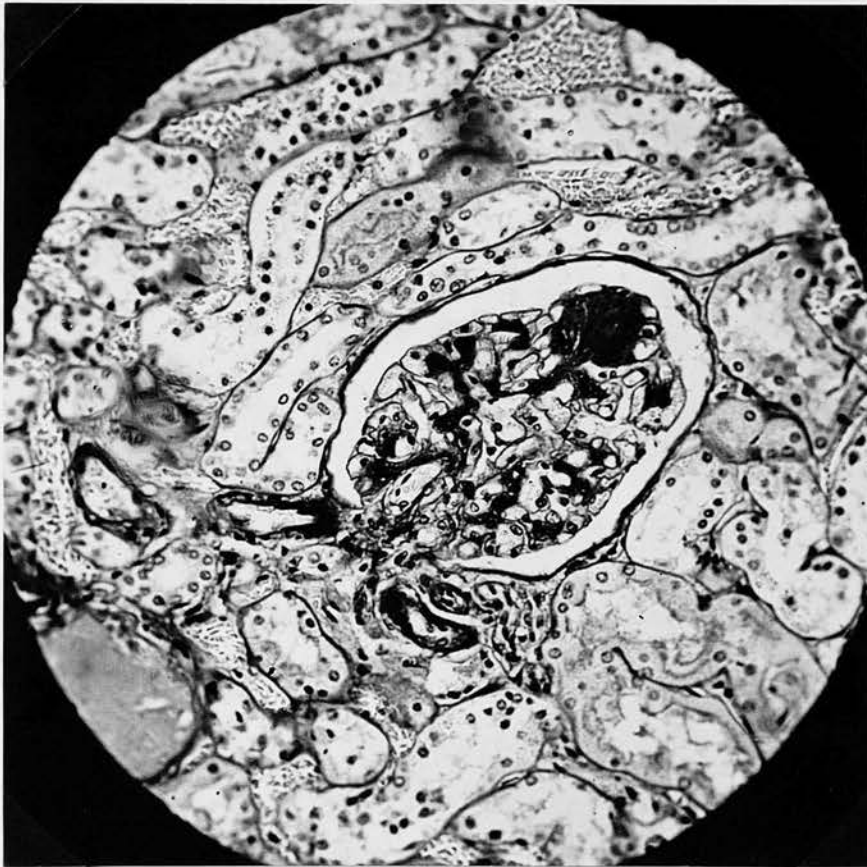
(b) a pronounced degree of arteriolosclerosis
(Fig. 4).



H + E X 490

Showing the pronounced degree
of arteriolosclerosis.

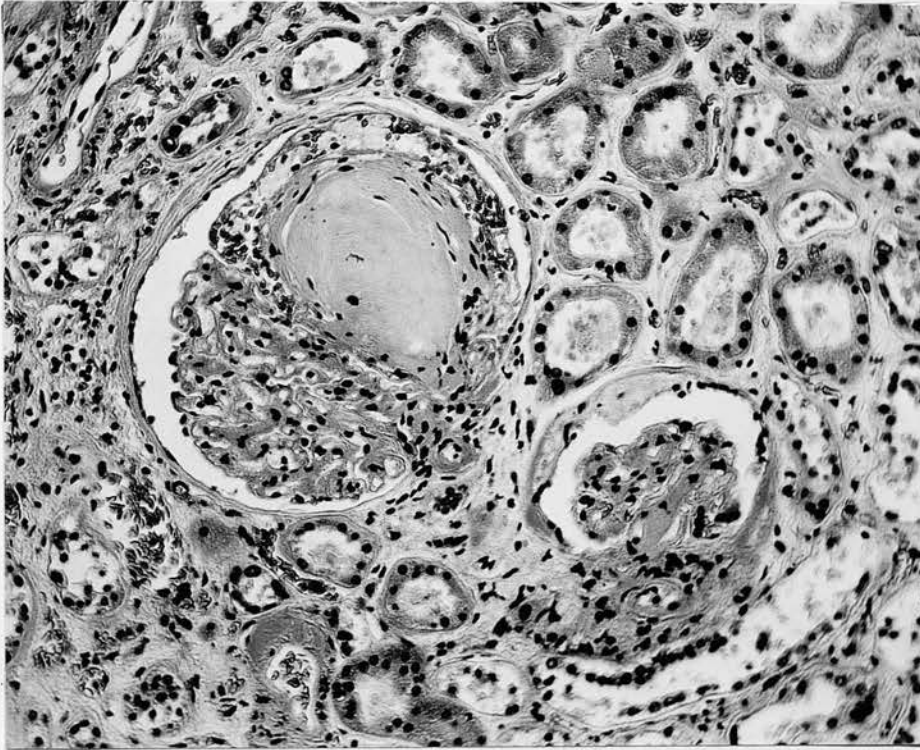
This arteriolosclerosis may be seen to affect both afferent and efferent arterioles (Fig. 5);



Periodic acid of Schiff X 230.

Shows that the arteriolosclerosis affects both afferent and efferent arterioles.

and (c) a hyaline cap on a thickened Bowman's membrane (Fig. 6).

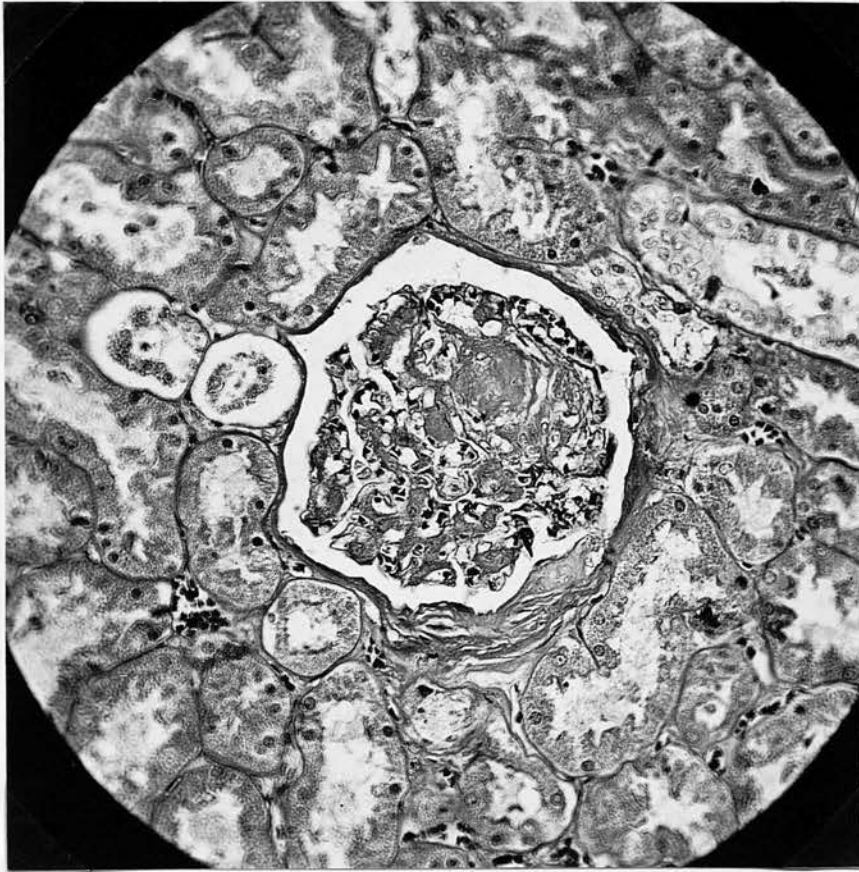


H + E X 205

A more advanced lesion, showing the thickening of Bowman's membrane.

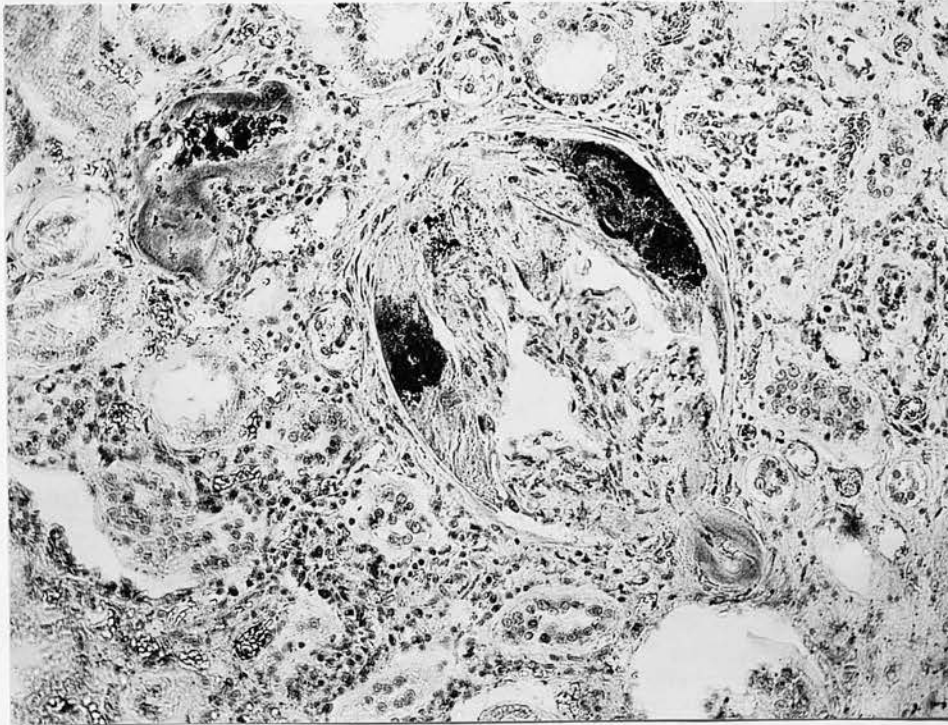
The smaller glomerulus shows a hyaline cap.

In some cases special stains were employed which showed the protein nature of the hyaline material (Fig. 7),



Coupled Diazo X 240.

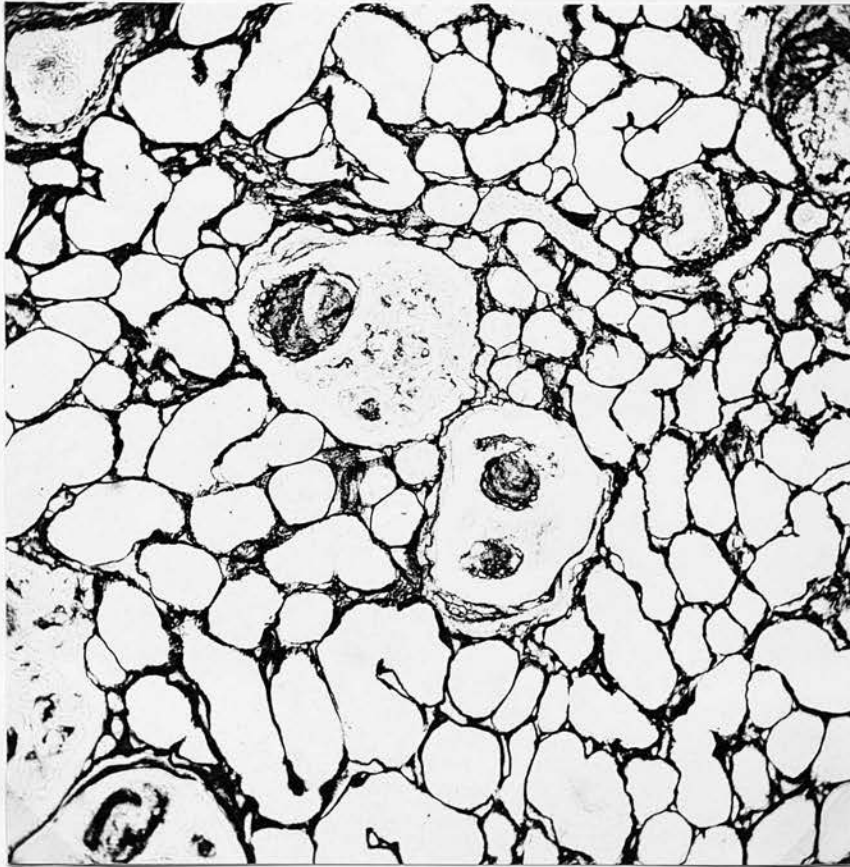
the fatty changes in it (Fig. 8),



Sudan IV X 205

Shows the intense fatty changes in
the "cap" and some fatty change in
the vessels and tubules.

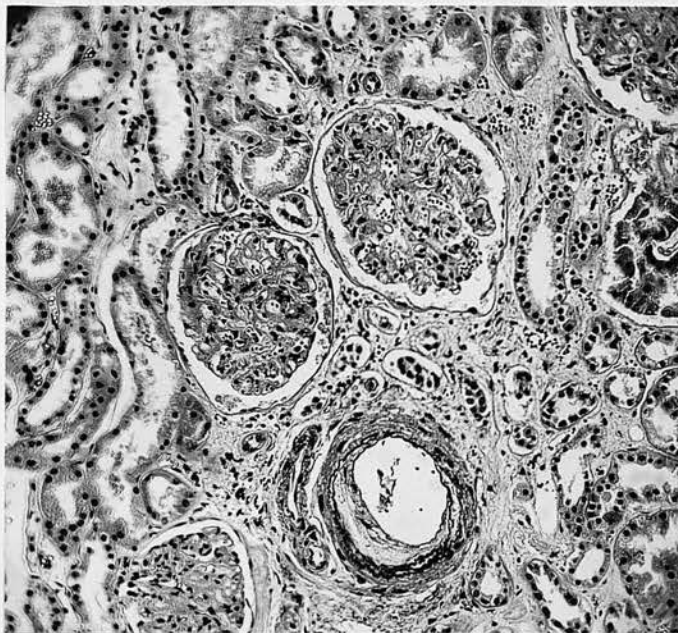
and the argentophil nature of the hyaline balls
(Fig. 9).



Sweets modification of Wilder X 145

Shows the argentophil nature of the
hyaline islands.

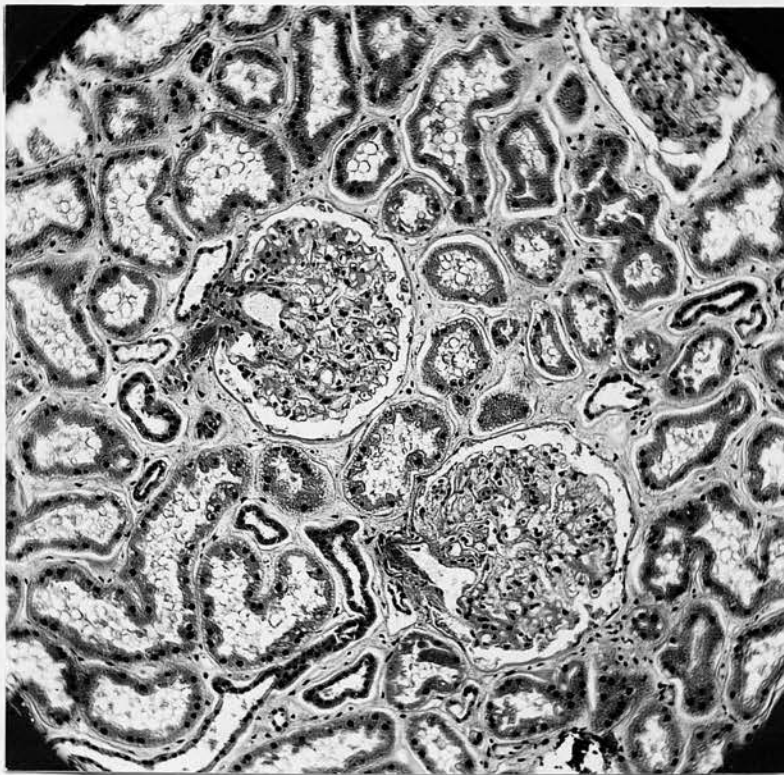
Group 2. The Arteriosclerotic Group (4 cases),
was composed of those cases showing arteriosclerosis,
both macroscopically and microscopically, but no
Kimmelstiel Wilson lesions. (Fig.10).



Van Giesen X 205

Arteriosclerotic kidney without
nodular Kimmelstiel Wilson lesions.

Group 3. The Arteriolosclerotic Group (3 cases)
consisted of those cases in which arteriolosclerosis
was present without the Kimmelstiel Wilson lesions.
(Fig.11).



H + E X 112.

Pronounced degree of arteriolosclerosis
without discrete hyaline islands.

Group 4. The Pyelonephritic Group (4 cases) consisted of those cases in which pyelonephritis was the dominant lesion and no lesions of Kimmelstiel & Wilson noted.

Group 5. The "other diabetic" Group (21 cases) included all the remaining cases which showed no more permanent renal change than "cloudy swelling", "fatty degeneration" or "toxic change".

RESULTS.

Comparison between the recorded clinical features of the 5 groups of renal pathology showed several differences. Each of the following tables shows the number of cases on which adequate observation was made. Although the numbers are small several of the differences appear to be significant, and attention is drawn below to those which seem to help to delineate the syndrome associated with Kimmelstiel Wilson lesions.

AGE & SEX (Table 1)

AGE & SEX					
	K.W.	Arterio-sclerotic.	Arteriolo-sclerotic.	Pyelo-nephritic.	Other Diabetics.
Number of cases.	11	4	3	4	21
Mean age at death.	69.1	69	52	48.2	51.2
Range	52-81	60-75	41-73	18-80	12-81
Number of females.	10	2	3	1	11
Number of males.	1	2	-	3	10

Our age and sex distribution agrees with many previous observations that the condition involves particularly the elderly female.

DIABETES.

An attempt was made to classify the diabetes according to its severity and controllability, as far as the available records permitted. Cases which had been satisfactorily controlled for long periods without insulin were considered mild; those which always required more than 20 units of insulin daily were considered severe; the remainder formed an intermediate group. Patients whose symptoms disappeared, who gained and maintained weight without incident were considered easily controlled; those whose symptoms recurred or who needed more than an initial hospital admission for stabilisation or coma were considered difficult to control;

the remainder formed an intermediate group.

(Table 2.)

DIABETES					
	K.W.	Arterio-sclerotic.	Arteriolo-sclerotic.	Pyelo-nephritic.	Other Diabetics.
Number of cases.	10	3	3	4	21
Duration in years.	6.4	2.3	4+	7	3.3
Nº severe cases.	3	-	2	2	7
Nº mild cases.	6	2	-	1	8
Nº easy to control	5	3	-	-	7
Difficult to control.	2	-	1	4	7

No clear difference could be distinguished between these small groups but it is worth noting that the Kimmelstiel Wilson group had both severe and mild cases, some easily controlled and others not.

There were no severe diabetics in the arterio-sclerotic group and all the pyelonephritic group were difficult to control.

PROTEINURIA (Table 3).

ALBUMINURIA					
	K.W.	Arterio-sclerotic.	Arteriolo-sclerotic.	Pyelo-nephritic.	Other Diabetics.
Number of cases.	10	3	3	4	21
Albumen present.	10	3	3	4	6
More than one plus.	7	-	2	3	1

All the groups with renal pathology had proteinuria, but none of the "other diabetics" had except in tests during their terminal coma. The Kimmelstiel Wilson group tended to show a heavy and persistent proteinuria, as did the pyelonephritic group.

URINARY TRACT INFECTION.

Infection was judged to be present if a catheter specimen of urine showed pus cells and gave a positive culture, or where there was post mortem evidence of inflammatory change. (Table 4).

URINARY INFECTION					
	K.W.	Arterio-sclerotic.	Arteriolo-sclerotic.	Pyelo-nephritic.	Other Diabetics.
Number of cases.	10	3	3	4	21
Nº with + culture or P.M. proof.	6	2	2	4	4
Nº in which contributed to death.	1	-	-	4	-

More than half the Kimmelstiel Wilson cases had an additional infection, while fourteen of the cases with renal pathology showed infection as well.

RENAL FAILURE AND ANAEMIA (Table 5)

RENAL FAILURE & ANAEMIA					
	K.W.	Arterio-sclerotic.	Arteriolo-sclerotic.	Pyelo-nephritic.	Other Diabetics.
Blood Urea. Nº of cases	5	2	3	3	9
Value above 100.	1	1	1	1	3
Urea Clearance Nº of cases	4	-	-	-	1
Value below 50%	3	-	-	-	1
Anaemia Nº of cases	6	1	3	3	9
Hb. less than 70%	2	-	1	-	2

There were insufficient observations to draw comparisons between one group and another. Three of the Kimmelstiel Wilson cases showed Urea clearance value below 50% and 2 had Hb. below 70%

HYPERTENSION (Table 6).

HYPERTENSION					
	K.W.	Arterio-sclerotic.	Arteriolo-sclerotic.	Pyelo-nephritic.	Other Diabetics.
Number of cases.	10	3	3	4	21
Nº with Hyper-tension.	9	3	1	1	4
Mean Blood-Pressure.	182 96	187 102	144 82	132 77	148 76

The one Kimmelstiel Wilson case which was not recorded to have hypertension, on the standard of 150/90 as the upper limit of systolic and diastolic pressure respectively, was admitted in heart failure from which she did not recover. At post mortem her heart weighed 410 gms. and had two myocardial infarcts, so it seems reasonable to assume that she had previously been hypertensive.

HEART FAILURE. (Table 7)

HEART FAILURE					
	K.W.	Arterio- sclerotic.	Arteriolo- sclerotic.	Pyelo- nephritic.	Other Diabetics.
Number of cases.	10	3	3	4	21
Nº with recorded failure.	8	1	1	~	1
Nº with nocturnal dyspnea.	3	~	1	~	~
Nº with raised J.V.P.	6	~	1	~	1
Nº with palpable liver.	4	1	1	1	2

Thus clinical signs of heart failure were common findings in the Kimmelstiel Wilson group, and much less common in other groups.

PERIPHERAL NEUROPATHY.

Peripheral neuropathy in the diabetic is frequently without easily demonstrable physical signs. The subjective criteria were complaints of darting or lancinating pains, or parathesia such as burning numbness or tingling in the limbs. The objective criteria were the presence of muscle tenderness or sensory loss, or absent jerks. (Table 8).

PERIPHERAL NEUROPATHY					
	K.W.	Arterio-sclerotic.	Arteriolo-sclerotic.	Pyelo-nephritic.	Other Diabetics.
Number of cases.	10	3	3	4	21
Subjective symptoms	8	1	2	-	-
Defective tendon-jerks.	9	2	2	-	5
Objective sensory changes.	2	-	-	-	-

Thus either subjective or objective evidence had been recorded of peripheral neuropathy in all but one case of the Kimmelstiel Wilson group.

EYE CHANGES

(Table 9).

EYE CHANGES					
	K.W.	Arterio-sclerotic.	Arteriolo-sclerotic.	Pyelo-nephritic.	Other Diabetics.
Number of cases.	10	3	3	4	21
Retinitis or Cataract.	10	-	1	4	6
Cataract.	6	-	1	-	4
Retinitis.	7	-	-	1	2

Eye changes were a feature of all Kimmelstiel Wilson cases, retinopathy being present in all cases in which the fundus was not obscured by cataract. In three cases it was sufficiently severe to make the patient "virtually blind", in contrast to the infrequent and relatively symptomless eye changes in the other groups.

OEDEMA. (Table 10)

OEDEMA					
	K.W.	Arterio- sclerotic.	Arteriolo- sclerotic.	Pyelo- nephritic.	Other Diabetics.
Number of cases.	10	3	3	4	21
No with oedema.	10	~	2	~	3
Ankles or Sacrum.	10	~	2	~	3
Oedema of arms.	4	~	~	~	~
Oedema of face.	2	~	~	~	~

All the cases of Kimmelstiel Wilson group had oedema, at least of the dependant parts, whilst in four it was recorded as extending beyond the legs and sacrum.

MAJOR CAUSE OF DEATH.

This was determined by close examination of the terminal clinical state in conjunction with the post mortem findings. (Table 11)

MAJOR CAUSE OF DEATH					
	K.W.	Arterio-sclerotic.	Arteriolo-sclerotic.	Pyelo-nephritic.	Other Diabetics.
Nº of cases.	11	4	3	4	21
Uraemia.	1 *	1	~	~	~
Hypertensive failure.	3	1	~	~	~
Myocardial infarct.	2	~	1	~	~
Infection.	~	~	~	3	8
Coma.	2	1	2	~	9
Unrelated.	3	2	~	1	4

* Pyelonephritis in addition.

Thus uraemia, heart failure and myocardial infarction only account for death in this series in cases which have sustained renal damage.

SUMMARY. (Table 12).

SUMMARY					
INCIDENCE ~	K.W.	Arterio-sclerosis.	Arterio-sclerosis.	Pyelo-nephritis.	Other Diabetes.
Number of cases.	11	4	3	4	21
Average age.	69.1	69	52	48.2	51.2
Number of females.	10	2	3	1	11
SUGGESTIVE ~					
Number of cases.	10	3	3	4	21
Duration in yrs.	6.4	2.3	4+	7	3.36
Diabetes: N° mild.	6	2	~	1	8
Easy to control.	5	3	~	~	7
Percent. Albuminuria:	10	3	3	4	6
Heavy.	7	~	2	3	1
Urinary Infection.	6	2	2	4	4
Hypertension.	9	3	1	1	4
PROBABLE ~					
Oedema.	10	~	2	~	3
Heart failure.	8	1	1	~	1
Periph. neuropathy.	9	2	2	~	5
Eye changes.	10	~	1	1	2

Thus, hypertension with heart failure, peripheral neuropathy, eye changes and oedema seemed to distinguish the Kimmelstiel Wilson group from the others. In no other case were these features found together, whilst they are almost universally present in the cases which showed Kimmelstiel Wilson lesions.

DISCUSSION, of analysis of PATHOLOGICAL MATERIAL.

Attention has recently been drawn to the fact that the kidneys of the diabetic are particularly vulnerable and liable to more than one type of disease. The material reviewed in this chapter showed that, of the 43 consecutive cases of fatal diabetes reviewed in this paper, 51% had irreversible kidney pathology, 25% showed intercapillary glomerulosclerosis, often in addition to evidence of arterial disease and infection, while 42% showed evidence of urinary infection. Millard & Root (1948) found that 52% of 110 diabetic autopsies showed well-marked kidney disease, and that in 23.5% there were 2 or more forms of renal disease apparent; 13.6% showed well-marked intercapillary glomerulosclerosis; and 12% had active pyelonephritis. Bell (1946), in his monograph on renal disease, has shown that renal arteriosclerosis is five times as frequent in the diabetic over 50 as in a control group of a similar age. In addition, after the age of 50, the small renal arteries also showed more severe intimal involvement in diabetics than in the control group. Joslin (1946) states that acute glomerulonephritis is uncommon in the diabetic. He quotes only one case. He does not give statistics of the occurrence of chronic glomerulonephritis, but states that it is commonly seen in a nephrotic stage, unfortunately

followed in the young diabetic within a period of months or years by the terminal phase of hypertension, nitrogen retention and uraemia. Pure nephrosis with complete recovery has not yet been seen in his diabetic patients. Baldwin & Root (1940) found renal infection at autopsy 5 times as frequently in diabetics as in other post mortems, and Robbins & Tucker (1944) showed that 7.3% of 307 diabetic autopsies showed acute pyelonephritis as the cause of death, as these authors point out that renal infection, for many years considered a minor complication, is a relatively important cause of death in the diabetic. Harrison & Bailey (1942), after reviewing their cases of necrotising renal papillitis, comment that the severity, rapid progression, and extent of necrosis of renal tissue were hardly to be found in the absence of diabetes. The incidence of intercapillary glomerulosclerosis has been given in varying figures according to the pathological interpretation, but Kimmelstiel & Porter, summarising the literature, find that the nodular lesions as originally described are present in 17% of diabetic post mortems.

This study has made no assessment of whether intercapillary glomerulosclerosis is peculiar to diabetics. Several authors have confused the position by recognising of diffuse glomerular hyalinisation, not peculiar to the diabetic, as

Kimmelstiel Wilson lesions of lesser grades. Goodof (1945) found "extremely mild lesions" in 10% of non-diabetics, clearly indicating that he regards as mild those lesions in which there are no hyaline islands. It is probable that Horn & Smetana (1942), who are the only observers to find a greater percentage in non-diabetics were similarly misled by their histological interpretation as they declare that in its "advanced" and presumably nodular form, the lesion was always associated with diabetes, but they do not give criteria for their less advanced forms. On the other hand, very occasional cases have been reported which showed all the pathological criteria of typical Kimmelstiel Wilson lesions and yet were not known to be diabetic. Whether such lesions are quite peculiar to diabetics or not, most recent authors agree with Bell that the "nodular lesions" are almost pathognomic of diabetes. Bell has seen only one exception, a patient with primary hypertension who was studied for several months before death and at no time showed either hyperglycaemia or glycosuria. Kimmelstiel & Porter also mention that exceptions have relatively rarely been observed - cases in which evidence of diabetes was absent although the renal lesion was fully developed. At the same time they quote a personal communication from Dr. A. C. Allen "I am altogether convinced of the specificity of the nodular lesion."

It is possible that a number of these cases are similar to the 3 reported by Rifkin, Parker, Polin, Backman & Spiro (1948). In these three, the diabetes was so mild that the diagnosis had to be established by glucose tolerance test. In two of them, the attention was directed to the possibility of diabetes by the presence of the other clinical manifestations. Kimmelstiel & Porter also add that identical lesions occur in a significant number of cases of glomerulonephritis without diabetes. However on this point, Bell comments "The diabetic nodular lesions must not be confused with the central hyaline masses characteristic of chronic glomerulonephritis. These are sometimes very prominent. The nephritic lesions are uniform throughout the glomerulus and never appear as separate discrete nodules as do the diabetic lesions".

Recent studies have also tended to confirm that a clinical syndrome is associated with these lesions. The original paper of Kimmelstiel & Wilson noted a number of clinical features common to their eight cases. They were elderly, hypertensive, with oedema, albuminuria and often heart or renal failure. Newburger & Peters, after reviewing the literature, came to the conclusion that many of the features would "warrant grouping them together as a distinctive disease pattern, of which the constant features are diabetes, albuminuria hypertension and retinal vascular disease". They

thought that a nephrotic syndrome was common, and that heart failure, when present was mainly left-sided and on a hypertensive basis. The review of Kimmelstiel & Porter claims that "in a patient 50 or more years of age with chronic diabetes, nephrotic oedema and albumen in the urine with a high blood cholestrol, one can safely make the diagnosis of intercapillary glomerulosclerosis, with 100% accuracy". They also say that "advanced retinopathy, specifically of the diabetic type, is more or less regularly associated with intercapillary glomerulosclerosis, and should be added to the complex syndrome associated with the glomerular lesion". They say that the difficulty of recognising early, or less advanced lesions, does not interfere with the concept of intercapillary glomerulosclerosis as a clinico-pathological entity.

Among our cases with Kimmelstiel Wilson lesions all the previously mentioned clinical features and some others were present in the terminal syndrome. Our method of study, however, has emphasised that some of the features listed by several authors as part of the syndrome, are also common in diabetics suffering from other renal pathology.

This includes proteinuria and other indices of impaired renal function. Proteinuria was frequently heavy in the Kimmelstiel Wilson cases, but

this finding was also common to the other groups.

In particular infection, which is frequent and often asymptomatic (Harrison & Bailey), was more commonly found in diabetic with other renal pathology.

Edmonson, Martin & Evans (1947) found Kimmelstiel Wilson lesions in 12 out of 26 diabetics with necrotising renal papillitis. Hence the finding of an infection, far from excluding other types of renal disease as Gauld, Stalker & Iyall (1948) would seem to suggest, should enhance the suspicion that other lesions are present.

Our pathological series did not include examination of the urine for doubly refractile bodies which Derow, Altschule & Slesinger (1939) suggested might be of diagnostic value, and which Rifkin et al. found to be an important differential point. This point will be examined in the clinical series.

There were no cases of nephritis in our pathological series. Newburger & Peters pointed out that the nephrotic stage of chronic glomerulonephritis is more likely to occur in a younger age group, and to give a characteristic history of previous acute onset. Henderson, Sprague & Wagener (1947) differentiated between glomerulonephritis and Kimmelstiel Wilson lesions. They found that in glomerulonephritis the main differences

lay in age groups, which tended to be younger, with an average age of 32; that the oedema tended to be greater and the albuminuria more severe, anaemia tended to be severe, retinopathy if present was hypertensive in character; and that the usual duration was only 1 - 4 months. Kimmelstiel & Porter thought that glomerulonephritis was rarely a problem in patients of the older age group, and thought these differences were quantitative rather than qualitative ones. However Kimmelstiel & Porter felt that repeated Addis counts should certainly enable the diagnosis of glomerulonephritis to be made for in that connection red cells would appear in pathologic numbers in contrast to the lack of haematuria of significant degree in glomerulosclerosis. This point will be studied in the clinical series. Amyloid disease was rare in diabetes (Newburger & Peters) and the absence of hypertension, the characteristic cachexia and anaemia, as well as the symptoms referable to the primary disease, should serve to differentiate this condition. Finally kidney failure is not a common termination. Only one of our series died of uraemia, a case complicated by gross infection. Kimmelstiel & Porter's review showed that only a small percentage 17.7% died of uraemia.

However, the following additional clinical features seem to distinguish diabetics with the Kimmelstiel Wilson lesions from diabetics with other renal pathology. Practically all the cases of our Kimmelstiel Wilson group showed a combination of:

1. Hypertension with heart failure.
2. Peripheral neuropathy.
3. Oedema at least of the dependant parts.
4. Retinopathy where the retina was not obscured by cataract.

It is striking how rare these features were in other groups of renal pathology studied. In no other case were all four features present in the same patient. We believe it to be significant that these four points only occurred together in the cases found to have Kimmelstiel Wilson lesions and that their presence implies the existence of Kimmelstiel Wilson lesions when found in a diabetic. The experience of others seems to confirm this view.

Hypertension with heart failure was noted to be present in the brief clinical notes accompanying the original pathological studies of Kimmelstiel & Wilson. Siegal (1940) and Siegal & Allen (1941) thought that marked hypertension and heart failure were common. On the other hand, Kimmelstiel & Porter, summarising the literature, found that

hypertension was not an essential feature but was probably a question of the duration of the disease and was correlated with the accompanying arteriosclerosis. Rifkin et al. in a similar series of cases of Kimmelstiel Wilson syndrome followed to autopsy, found that 95% had systolic hypertension, 90% diastolic hypertension, and 93% were observed to have been in heart failure. Two of those who did not show hypertension had histories and E. C. G. evidence of recent myocardial infarction. On the other hand, Mann et al. (1949) choosing their cases deliberately from younger cases, thought that although hypertension was a universal sign, it did not become severe until late in the disease.

Peripheral neuropathy. Siegal, and Siegal & Allen, first described peripheral neuropathy as part of the syndrome, attention apparently being drawn to the nervous system by the presence of a case of pseudo-tubes in their series. Others, such as Rifkin et al. have noted simply that peripheral neuropathy was a complication, but do not give details of their records. In our series, we found that subjective symptoms, coupled with absent jerks were an almost universal finding. The type of neuropathy present in our series would probably be considered "ischaemic neuropathy" in the classification of Treusch (1945). Earlier Woltman &

Wilder (1929) demonstrated a well-marked hyalinisation of the arterioles accompanying peripheral nerves in diabetic neuropathy. It is interesting to note that Rundles (1945) found that 43 of 125 cases of diabetic neuropathy had retinal disease of a characteristic diabetic type, and that he thought that the coincidence of these two diabetic complications appeared to be more than "fortuituous".

Oedema. Kimmelstiel & Wilson described the finding of widespread oedema, greater than to be accounted for by heart failure, as one of the clinical aspects of their cases, four of their eight cases having generalised oedema. Newburger & Peters thought that a nephrotic syndrome was common. Several case reports have been made of patients with "full nephrotic syndrome" such as Derow et al. However Herbut (1941) described 10 cases with only one nephrotic syndrome, and only 3 of the 10 advanced cases of Siegal & Allen had generalised oedema. Laipply, Fitzen & Dutra (1944), who considered that the nephrotic syndrome could be diagnosed by the presence of a 3-4 plus albuminuria, generalised oedema involving the face and body, and total plasma proteins below 6 gs%, found it present in 6.5% of cases. Only one of our series could fit their criteria. Kimmelstiel & Porter, summarising the literature, found oedema of a nephrotic type in

less than 10%. Recently Mann et al. have suggested that hypoproteinaemia is a relatively late and generally a terminal finding, but that oedema was an early sign, and in females, often the first. Our series, as those of Rifkin et al. would suggest that the presence of oedema, even if limited to the dependant parts, is significant in conjunction with the other evidence.

Retinopathy. Newburger & Peters found retinopathy present as a universal sign in all their cases and this observation has met with more or less general confirmation since. Indeed, Kimmelstiel & Porter in their summary say that "advanced retinopathy, specifically of the diabetic type is more or less regularly associated with intercapillary glomerulosclerosis, and should be added to the complete clinical syndrome associated with the glomerular lesion". They take the view that retinopathy precedes the renal change and is more closely related to the diabetes than to the vascular or glomerulosclerosis. Their analysis of the literature shows it to have been recorded in 86% of the cases to that date. Their findings were those of ophthalmoscope examination, however, and recently Ashton (1949) has suggested that microscopic examination of the retina at autopsy would probably show an even higher incidence. He confirms the observations of

Ballantyne (1946) that microaneurysms can be found in some cases of diabetes only on microscopic examination, which Ballantyne called the "sub-clinical stage" of diabetic retinopathy. Earlier, von Bahr, (1947) discussing diabetic retinopathy of the proliferating type, had suggested that renal damage was almost part of the morbid picture. He quoted a personal communication from H.P. Wagener that a special type of renal disturbance, the Kimmelstiel Wilson lesion, is associated with this severe retinopathy and inclined to the same view himself. Henderson et al. found that "advanced retinopathy is more or less regularly associated with intercapillary glomerulosclerosis". Sphüler & Zollinger (1943) suggested that the same pathological conditions are present in the retina as in the kidney. Recently, Ashton, by careful digestive and staining reactions has produced convincing evidence to support his view in "complete agreement with Friedenwald's (1948) opinion that intercapillary glomerulosclerosis and diabetic retinopathy are manifestations of the same vascular process".

It is generally agreed that the syndrome is most commonly found in the elderly mildly diabetic female, yet none of these other features are of diagnostic significance.

Kimmelstiel & Porter, discussing the type of diabetic in which these lesions are found, showed

that the majority of cases occurred between the ages of 50 and 70 and that females were twice as often affected as males. Cases have, however, been recorded in younger age groups, by Laipply et al. at 16, Goodof at 17 and 19. The recent series of Mann et al. selected to have an onset of diabetes before the age of 30, showed a lower age group and males were twice as commonly affected as females in their series.

Whilst most of the cases occur in the mild diabetic, some of our cases and those of Herbut, show that this is not necessarily so. Mann et al. in their series thought that the diabetes was severe. Kimmelstiel & Porter have already pointed out that the age group in which most cases occur is one in which most diabetes is of a mild nature, and hence most recorded cases are also of mild nature. The question of control is more difficult to assess, depending as it does on very long-term continued observations. There is no satisfactory evidence on which to base an opinion of control, other than the frequency of gross manifestations of symptoms, coma of hypoglycaemia. There has always been a clinical impression that the badly controlled diabetic was more likely to suffer from complications such as neuropathy. Rundles, discussing control in his paper on neuropathy, says that "although

the retinal changes are not dependent on either albuminuria, renal disease or hypertension, there are many clinical reasons for suspecting that all these have a common aetiology in some blood vessel abnormality complicating uncontrolled diabetes". Yet a common finding of other investigation is that there is no correlation between the control of the diabetes and the onset of intercapillary glomerulosclerosis. Laipply et al. found no correlation. Henderson et al. thought that the control of diabetes had very little effect; Kimmelstiel & Porter that the treatment of the diabetes had no bearing on the renal involvement.

The duration of the diabetes, though also difficult to assess, seems to be important. It is true that a number of cases have been recorded in which diabetes was only discovered in the patient's last illness, as in some of the cases of Rifkin et al. However, Henderson et al. showed that where in their series, the duration of the diabetes appeared to be short, the nature of the diabetes was mild, and may well have been present without symptoms for some time. Their series showed that when advanced lesions were present, the duration of diabetes averaged 11.2 years, where mild lesions were present 8.1 years, and where no lesions were present 5.2 years. Goodof showed a steady rise in the

incidence of intercapillary glomerulosclerosis amongst diabetics arranged in order of duration after six years had passed. Mann et al. also found a significant relation of the lesion with duration of diabetes, the average duration of their younger group of diabetics being 14.8 years. Dolger (1946) put forward the view that the duration of diabetes was the most important factor in the development of degenerative lesions. Yet Croom & Scott (1949) could find no correlation between the severity and control of diabetes and the onset of complications, and showed clearly that degenerative lesions were not inevitable. Their study of 60 diabetics of long duration averaging 18.7 years, showed 15 free from any degenerative disease, one of whom had been diabetic for 26 years. In their group there were only 2 with albuminuria and oedema. Thus if degenerative complications are not inevitable with prolonged diabetes and, less certainly, control makes little difference then some other factor may be involved. These complications may be due either to prolonged diabetes in some special circumstances with which we are not as yet familiar, or to prolonged diabetes of a special type.

Conclusions from Chapter One.

A comparison of the clinical features of 43 diabetics who were grouped according to their renal pathology showed that

a. The Kimmelstiel Wilson group comprised especially elderly females who had been mildly diabetic for many years, and who were, or had been hypertensive.

b. All groups with renal pathology were associated with proteinuria and, more frequently than other diabetics, with urinary infection.

c. The Kimmelstiel Wilson group, however, almost universally showed in addition all the following features.

Hypertension with heart failure.

Peripheral neuropathy.

Oedema at least of the dependant parts.

Retinopathy or cataracts obscuring the retina.

This syndrome was not found in any other group. It was therefore concluded that, in diabetics who showed proteinuria, the presence of the additional features listed above would justify the conclusion that Kimmelstiel Wilson lesions exist in the kidneys. On this basis a search was made for such cases amongst the patients attending or in hospital, and the results of their study follows in the next chapter.

CHAPTER 3.

ANALYSIS OF CLINICAL MATERIAL.

The clinical features discussed in Chapter 1 were then used to identify cases of the fully developed Kimmelstiel Wilson syndrome amongst the patients in hospital or attending the diabetic clinic. The nature of the diabetic clinic has probably some bearing on this, so the age and sex distribution of the clinic (525 patients at that date) was computed.

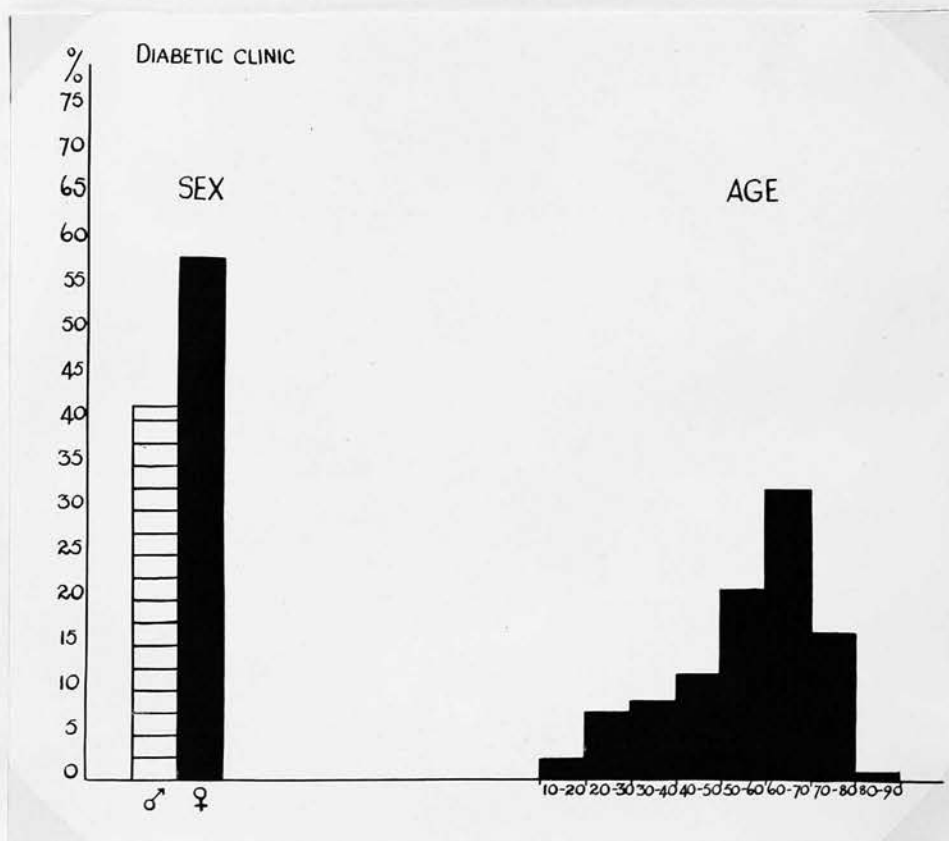


Fig. 12

Nine cases were found which fulfilled the requirements of the syndrome. Five cases were found which showed arteriosclerosis and albuminuria only.

There was one case of chronic glomerulonephritis. The relevant points from their case histories are attached in Appendix B.

Of the nine cases of Kimmelstiel Wilson syndrome two have since come to autopsy and the clinical diagnosis was confirmed.

Three presented for the first time with fully developed syndromes. Seen for the first time at this stage they certainly gave the impression of a distinctive disease pattern. The remaining cases have been under observation for periods varying between 2 and 6 years.

Proteinuria was observed in 5 out of these 6 from their first attendance, whilst the sixth developed proteinuria early in her attendance. This appears early as a variable trace and gradually increases in amount, becoming permanent and massive as Mann et al. found.

Urinary infection was easily controlled by chemotherapy, in most cases, but in case 24 it certainly contributed to the fatal outcome.

Oedema was also an early symptom, and in one case (case 31) was unexplained for a considerable time. It seems to have been intermittent at first, tending to be more regularly present in the later stages. Hypoproteinuria was only found to any extent in one case..

The presenting symptom in two cases was failing vision, and the severity of the eye changes in all nine cases was remarkable.

The presenting symptom in three cases was peripheral neuropathy in one case so severe as to be classed as pseudo-tabes.

In the six cases hypertension was not present when they first came under observation, but developed as the disease progressed. In one case (case 31) the progress was remarkably rapid, and in all it has shown a fairly constant progression. Heart failure where it occurred, was remarkably responsive to rest, digitalis and salt free diet.

The main difficulty encountered in the differential diagnosis was presented by the arteriosclerotic group. This group was characterised by the presence of gross arteriosclerosis and hypertension. Oedema was only present if in failure, and cleared as the failure disappeared. None of them showed retinopathy of a diabetic type which was the most useful differential point. None showed peripheral neuropathy.

One case of chronic glomerulonephritis was encountered. She was much younger, gave a clear history of an acute onset with haematuria, oedema of the face and hypertension, which settled, leaving her with a constant albuminuria. Apart from the clear-cut history, and the absence of subjective signs of

peripheral neuropathy and the absence of heart failure, the picture is remarkably like that of the Kimmelstiel Wilson syndrome.

Conclusion from Chapter 3.

The clinical material would suggest that the natural history of the disease would begin in a diabetic with traces of albumen in the urine, coupled with visual defects or symptoms of peripheral neuropathy to which oedema might be added very soon, and later hypertension, rising steadily to levels at which failure will supervene unless one of the other hazards of this condition brings the disease to a termination.

CHAPTER 4.

ANCILLARY AIDS.

The clinical material discussed in Chapter 3 was then subject to investigation by the following ancillary methods of investigation which might be of assistance in the differential diagnosis. In each investigation, a number of diabetics who did not show any evidence of complication were used as controls.

(1) Repeated Addis Counts.

Method:

The method described by Addis (1948) was employed. Seven Kimmelstiel Wilson cases, five arteriosclerotic cases and one case of glomerulonephritis were examined repeatedly. The results of cell and cast counts are shown in Table 13. The cells included white blood cells and renal epithelial cells. Bladder cells were not counted. If more than 2 red blood cells were noticed the fact is remarked upon. If pus was evidently present the fact is also noted and the pyuria was cleared before further observations were made. The casts were nearly all hyaline, but very

occasionally granular.

REPEATED ADDIS COUNTS			
	Case No.	Casts in 100,000's	Epithelial & wbc's Cells in millions
Kimmelstiel- Wilson lesion	25	1 0 3 0	12 (Pus) 2 1 5
	26	0 1 0 2	4 2 0 2
	27	4 0 2 1	120 (Pus) 3 0 0
	28	5 0 2 0	5 3 3 2
	29	1 0 0 1	2 0 2 1
	30	2 1	3 0
	31	10 4 0 4	14 (Pus) 2 0 1
Chronic Glomerulo- nephritis	37	4 2 2 2	14 (r.b.c's) 4 6 24 (r.b.c's)

Table 13.

Pyuria was accidentally discovered by these means in two diabetics who were symptomless, and this was cleared by chemotherapy. Apart from this valuable information, the counts in the Kimmelstiel Wilson and arteriosclerotic cases yielded no information of value especially in view of the time-consuming nature of the procedure.



However, the case of chronic glomerulonephritis did show an excess of red blood cells on two occasions and perhaps, but less certainly, a more constant number of casts.

(2) Quantitative estimation of Proteinuria.

Method:

The method of Addis was not used as it was found to give a different and usually higher figure on morning urines, than that obtained by measurement of an aliquot of the total mixed 24 hour specimen. The method of King & Haselwood (1948) was used in the determinations. In all cases the results charted were obtained when heart failure was controlled and after urinary infection was cleared.

<u>ALBUMEN in Grams per 24 hours.</u>		
Kimmelstiel Wilson Cases	Case No.	Albumen in gms/ 24 hours urine
	23	2.8
	25	4.2
	26	5.9
	27	1.8
	28	8.2
	29	2.7
	30	3.0
Arterio- Sclerotic	31	3.9
	32	7.0
	33	0.88
	34	0.50
	35	1.2
	36	0.48
Chronic Glomerulo- nephritis	37	4.2

Table 14.

Thus the Kimmelstiel Wilson syndrome, when fully developed, shows a fairly severe albuminuria, 1.8 gms being the lowest value recorded per 24 hours. On the other hand, one of the arteriosclerotics and the case of chronic glomerulonephritis also showed a severe proteinuria. In addition, one of the Kimmelstiel Wilson cases (case 26) while in heart failure showed 19.8 gm/24 hours, which cleared to 5.9 gms. when the failure recovered.

(3) Doubly Refractile Bodies.

Method:

The method described by Rifkin et al. was followed. The doubly refractile bodies are very distinctive if good illumination is used. In one normal control curious shell-shaped bodies were discovered, with wide, poorly differentiated maltese crosses, badly illuminated even with a good source of light. They are quite distinct from the other doubly refractile bodies and were identified as yeasts.

Results:

The urines of 7 cases with the Kimmelstiel Wilson syndrome were examined, that of 5 cases of arteriosclerosis, and one case of chronic glomerulonephritis. The urine of 13 normal diabetics was also examined as a control on three occasions, and

the urine of three cases suffering from the nephrotic stage of glomerulonephritis without diabetes.

The results are shown in Table 15.

	DOUBLY REFRACTILE BODIES			
	CASE No.	PROFUSE	DOUBLY REFRACTILE CASTS	REQUIRING REPEATED OBSERVATIONS.
KIMMELSTIEL WILSON LESION	25	+	+	ALL +VE
	26	+	+	ALL +VE
	27	-	-	+ 2ND. ATTEMPT
	28	+	+	ALL +VE
	29	-	-	+ 3RD. ATTEMPT.
	30	-	-	+ 2ND ATTEMPT
	31	+	-	ALL +VE.

	No. OF CASES.			
ARTERIO-SCLEROTIC	5	NIL ON REPEATED ATTEMPTS		
CONTROL NORMAL DIABETIC	13	NIL. OCCASIONAL YEASTS IN ONE		
CHRONIC GLOMERULO-NEPHRITIS	1	NIL ON FOUR OCCASIONS.		
NON-DIABETIC NEPHROTIC SYNDROME.	3	PROFUSE 3	CASTS DOUBLY REFRACTED 1	REQUIRING REPEATED OBS. ALL +VE.

All the cases exhibiting a Kimmelstiel Wilson syndrome were discovered to have doubly refractile bodies in the urine. In four cases they were

profuse and were usually to be discovered in uncentrifuged fresh specimens. In three cases there were casts which had doubly refractile bodies embedded in them.

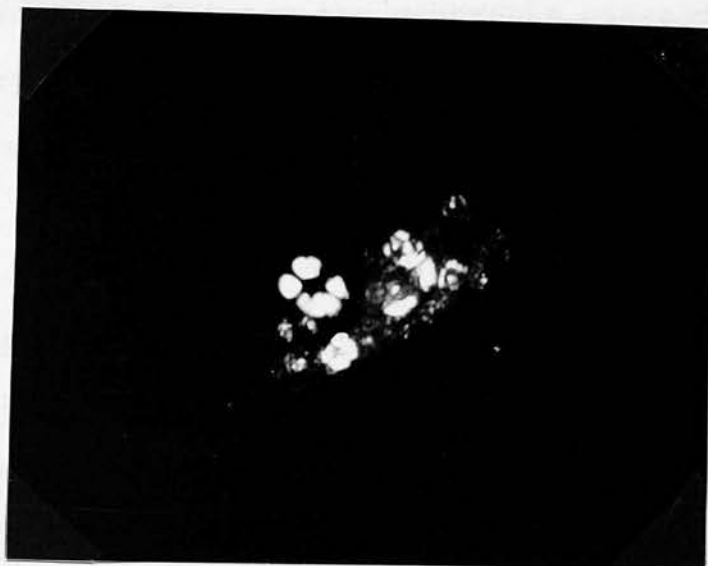


Fig. 13 shows one such cast X 665.

In three other cases repeated examination of centrifuged specimens had to be made before the doubly refractile bodies were identified in small numbers. None of the cases of arteriosclerosis showed these bodies. The one case of chronic glomerulonephritis did not show them on four repeated occasions.

On the other hand, the urines of three cases who were in the nephrotic stage of chronic glomerulonephritis without diabetes were examined and all

showed doubly refractile bodies.

It was therefore concluded that the presence of doubly refractile bodies in the urine is of considerable diagnostic help, as Rifkin et al. suggest. It is doubtful, however, if it could be used to differentiate between the nephrotic stage of chronic glomerulonephritis and the Kimmelstiel Wilson syndrome.

Conclusion from Chapter 4.

- (1) Repeated Addis counts may be of value in the differential diagnosis from chronic glomerulonephritis.
- (2) Quantitative measurements of the proteinuria per 24 hour urine are of some value as they are usually fairly high, but are also occasionally high in other cases of renal pathology, and are subject to aggravation by extrarenal causes.
- (3) Doubly refractile bodies in the urine are of considerable diagnostic importance, but may not differentiate between Kimmelstiel Wilson lesions and chronic glomerulonephritis.

CHAPTER 5.

Studies of Renal Clearances.

It was considered that the application of clearance techniques to the clinical cases might be of value in determining the degree of renal dysfunction, and at the same time would yield information which might enable comparisons between the renal thresholds of diabetics to be made.

Method:

Renal clearance techniques. Preliminary investigations showed that it was difficult and probably undesirable, to "load" the blood glucose by intravenous route. It seemed likely that circulatory overload might be encountered in elderly hypertensive patients, and the difficulties connected with the maintenance of a high level by accelerating the rate of infusion (Smith, H.W. 1943), while probably less in the diabetic would render the method cumbersome. It occurred to us that as the patients were diabetic, satisfactory blood levels could be maintained by the alimentary route. This proved to be the case. We followed

the blood sugar levels in 4 test patients.

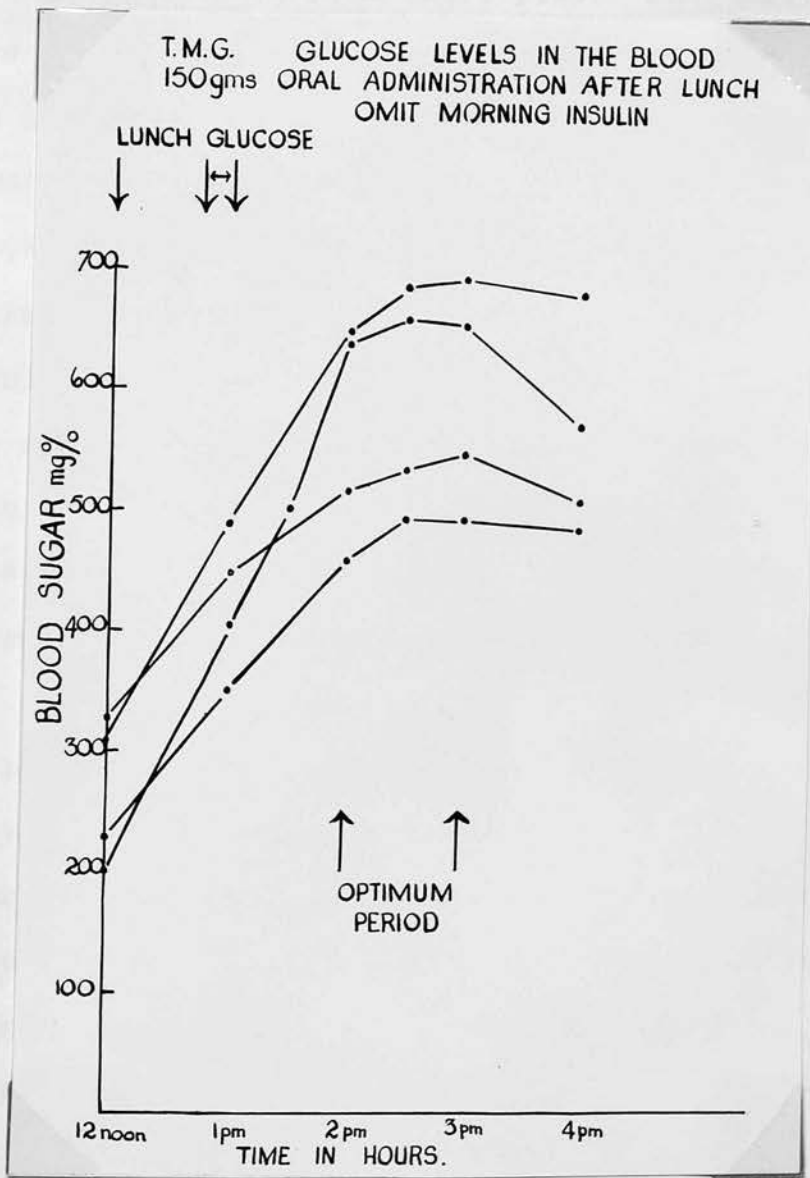


Fig. 14.

From this it will be observed that satisfactory levels were reached by omitting the morning insulin on the day of the test, and giving the patient 150 gms. of glucose within one hour of the midday meal. In patients who did not appear to be severe diabetics, a further load of 50 gms. glucose was given with the midday meal. On this basis a

satisfactory rising, but nearly constant level was obtained between 2 p.m. and 3 p.m. These levels were always above 380 mgs % and usually between 400 and 600 mgs %. Thus they fulfilled the specification of Goldring, Chasis, Ranges & Smith (1940). On two occasions, when the patients were very sick, satisfactory levels were not obtained and the results were therefore discarded. Soluble insulin was administered at the conclusion, and no difficulties were encountered in regard to the diabetes. This standard of dosage and timing was employed throughout the clearance observations.

Further, it was found that diabetic patients with this amount of glucose and with no fluid restrictions always passed more than 50 ml, often over 100 ml. urine in 20 minutes. Hence it was determined that, if 2 consecutive flow periods of 20 minutes each were used, then satisfactory levels of Para-amino-hippuric Acid and Sodium Thiosulphate could be maintained over this period by single priming dose, without the necessity of continuous intravenous maintenance.

Therefore, a standard technique was adopted as follows:

- 1) Omit morning insulin.
- 2) Lunch, 12 noon (supplement with 50 gms. glucose if necessary).

3) 150 gms. glucose, between 12.45 and 1 p.m.

dissolved in 1000 ml. water, but with no fluid restriction.

4) 1.30 p.m., patient catheterised. Aliquot preserved as "blank" specimen. The catheter is left in situ, draining into receptacle. A 20 ml. Sample of venous blood obtained as "blank", heparinised with a minute drop of heparin and centrifuged.

10 grams of Anhydrous Sodium thiosulphate, dissolved in 20 ml. pyrogen-free distilled water and autoclaved was then given intravenously. We find it necessary to give this injection very slowly, over the course of about 10 minutes, otherwise vomiting may be induced, which if severe, might prevent the blood glucose reaching and maintaining satisfactory levels.

Simultaneously 1 gram of Para-amino-hippuric acid, as sodium salt, dissolved in 5 ml. pyrogen-free water and sterilised by Seitz filtration is injected intramuscularly.

Twenty minutes is then allowed to pass for equilibrium to be established between the intracellular fluid and these substances.

The bladder is then washed out with 20 ml. of sterile normal saline with two washings. 60 ml. of air are then injected into the bladder and expelled by suprapubic pressure. This procedure is repeated and usually gives a good "end point". Thereafter

the first collection period begins.

After 20 minutes, when more than 50 ml. of urine have been obtained, the bladder is again washed and emptied by the same technique, the urine measured and an aliquot retained for analysis.

A similar collection is made over a second collecting period.

Venous blood samples are obtained either 2 minutes before midpoint, where this can be accurately anticipated, or a series of blood samples are taken, the results graphed and the figure interpolated allowing 2 minutes before midpoint for urine flow at this speed. These samples are immediately heparinised with a minute drop of heparin and centrifuged. Blood sugar samples are obtained by capillary pipette and placed immediately into copper sulphate tubes.

Clearances are calculated from the formula: $\frac{U V}{P}$

where U = urine concentration of thiosulphate, or para-amino-hippuric acid.

P = Plasma concentration of thiosulphate of para-amino-hippuric acid;

V = minute volume of urine.

Tmg = Tubular maximum reabsorption capacity is calculated from the formula:

$$Tmg. = P_g \times G.F.R. - U_g V$$

where P_g = Plasma Glucose per ml.

G.F.R. = Glomerular filtration rate in ml/min.

$P_g \times G.F.R.$ is therefore the load of glucose offered in the tubules for reabsorption.

U_g = Urine glucose in mgs/ml.

V = minute volume of urine.

The Threshold is calculated as the point at which the $T_{mg} = P_g \times G.F.R.$ because if the plasma glucose was to rise beyond this point then sugar would appear in the urine.

Therefore - The threshold $P_g = \frac{T_{mg}}{GFR}$

(a) Para-amino-hippuric acid estimation and interpretation of PAH clearances as a measure of Essential Renal Plasma Flow.

Goldring & Chasis (1944)

(b) Thiosulphate estimation and interpretation of thiosulphate clearance as measuring Glomerular Filtration Rate.

Newman, Gilman & Philips (1946)

(c) Glucose was estimated by the method of King & Garner (1947) in the routine laboratory.

(d) All analysis was done in duplicate and results of analysis with greater than 5% difference were rejected.

(e) All results were standardised to a square metre body surface of 1.73 sq. metres.

(f) All calculations were made by slide rule.

(g) The computation of Threshold values from renal dynamics has been a matter of dispute. The method of Mirsky & Nelson (1943) was essentially similar to the one here employed, except that they used $\frac{\text{Urea clearance}}{0.6}$ as a measure of Glomerular Filtration

Rate. Subsequently it has been shown that in the healthy kidney this is a reasonable assumption, but that in the diseased kidney the Glomerular Filtration Rate and urea clearance approximate, so this method was not considered satisfactory for cases likely to exhibit renal functional impairment. A method employing Sodium Thiosulphate for Glomerular Filtration Rate is obviously preferable in the diseased kidney. On the other hand, Ekehorn (1946) has doubted the existence of a tubular maximum reabsorption capacity in spite of the evidence of Shannon & Fisher (1938), Shannon, Farber & Troast (1941) and Smith (1943), mainly because he claims that thereby the thresholds are put too high, and do not agree with clinical findings.

It did not seem to us that this would in any way invalidate our comparison between the calculated thresholds of one group of diabetics and another, provided the same standard technique was used in all cases. At the same time, we felt it would be better if some explanation were offered for this discrepancy. On the one hand Shannon & Fisher have shown

that significant amounts of sugar may leak into the urine 10 to 20 mgs. below the level at which maximal rate of reabsorption is reached. This may be partly the explanation, but it seemed to us that it was possible that the amount of glucose which the tubules appeared to absorb might also be in part accounted for by the utilisation of sugar by the kidneys in their considerable work. A patient (a schoolmaster, H.H. age 58) with no signs of any degenerative process and with mild diabetes was investigated on these lines.

His renal clearance figures were:

E.R.P.F.	640 ml/min
G.F.R.	150 ml/min
Tmg	349 mg/min
$\frac{\text{GFR}}{\text{Tmg}}$ ratio	.43
Threshold	232 mgs %

A talkathine catheter was then passed under X-ray screen control into his right renal vein and simultaneous arterial blood samples obtained. An arterial-venous oxygen difference of 14 cc/litre was obtained, estimated by the Haldane method.

Now, his E.R.P.F. was 640 ml/min, his haematocrit 45%

Therefore, his Essential Renal Blood Flow was

1175 ml/min

Therefore, the oxygen consumption of his kidneys was

16.4 cc's/minute

Therefore, if we assume that the kidney uses glucose
for its energy,

and 100 gms. glucose = 75 litres of Oxygen

Then 16.4 cc of O_2 /min = 21.8 mgs glucose/min

metabolised and not reabsorbed

Therefore Calculated Tmg = 349 mg/min

less glucose utilised	21.8
and not reabsorbed	<hr/>

Actual Tmg	327.2
------------	-------

Therefore, Threshold	= 218 mgs %.
----------------------	--------------

It was felt that further investigation on these lines was called for as a possible explanation of the discrepancy between the calculated and the clinical threshold, but that the accepted procedures would be adequate for the present purposes. Further investigation is now being carried out.

RESULTS

The method was then used on 13 normal diabetics. They were free from albuminuria, retinopathy, hypertension and peripheral neuropathy and were clinically healthy apart from their diabetes. None had been in diabetic coma within 4 weeks of the estimation of renal function.

<u>NORMAL DIABETICS</u>						
<u>E.R.P.F.</u>	<u>G.F. R.</u>	<u>F.F.</u>	<u>Tmg.</u>	<u>G.F.R.</u> <u>Tmg</u> r.	<u>Threshold</u>	
705	114	.14	256	.445	224	
442	111	.25	183	.602	164	
751	129	.17	212	.625	164	
436	105	.24	297	.353	294	
621	105	.16	236	.445	225	
425	106	.25	294	.361	276	
765	133	.17	208	.638	156	
583	155	.26	308	.500	198	
728	135	.18	374	.362	276	
401	134	.33	377	.355	281	
640	150	.23	349	.430	232	
591	125	.21	281	.471	225	
555	119	.22	205.5	.580	174	
<hr/>						
<u>Mean</u>	586	124	.237	275	.474	222
<u>S. D.</u>	± 122	± 20.6	$\pm .058$	± 46.4	$\pm .013$	± 52.5
<u>100XS.D.</u>						
Mean	20.8	16.6	24.4	16.87	27.0	23.6

Table 16.

This shows that our technique showed normal renal function to be present in these normal diabetics as judged by renal clearance tests. Hogeman (1948) studying 12 diabetics without nephropathy, concluded that diabetes per se does not cause any demonstrable disturbance of renal function. Levin (1948) also found that there was no difference between the Tmg's of normals and of uncomplicated diabetics. The calculated thresholds are within the limits of normality calculated from the standards of Tmg. and GFR given by Homer Smith, yet they appear higher than the clinically observed threshold of 180. Thus we concluded that in the normal diabetic there was no demonstrable alteration of renal function.

The method was also used on 7 cases of Kimmelstiel Wilson syndrome.

DIABETICS with KIMMELSTIEL-WILSON SYNDROME

	<u>E. R. P.F.</u>	<u>G.F.R.</u>	<u>F.F.</u>	<u>Tmg</u>	<u>G.F.R.</u> <u>Tmg</u> r.	<u>Threshold</u>
	373	49.1	.13	106	.462	215
	264	76.2	.29	152	.496	200
	355	100	.28	286	.350	286
	266	81	.30	286	.284	352
	312	73	.24	287	.310	323
	195	64	.33	127	.500	204
	360	62	.18	170	.365	274
<u>Mean</u>	303.	72.	.25	202	.395	264
<u>S. D.</u>	± 62.8	± 15.6	$\pm .066$	± 75.3	$\pm .084$	± 59.8
<u>100X S.D.</u> <u>Mean</u>	20.7	21.6	26.9	37.2	21.3	22.6

Table 17.

The mean essential renal plasma flow is close to the essential renal plasma flow (diodrast) of 270.9 found by Hogeman in 12 cases of diabetes who showed constant proteinuria, elevated blood pressure and retinitis. The mean glomerular filtration rate is also close to that of 59.2 found by Hogeman in his series. The Tmg's, although reduced below the normal value, are yet less reduced than the glomerular filtration rates. The mean calculated threshold is thus in the upper range of the calculated thresholds observed in normal diabetics. The

thresholds observed were of the same order as those observed by Levin in two cases of diabetes with renal lesions, retinitis and hypertension, 240 - 260 mgs %. Thus we concluded that there is a significantly lowered renal function as judged by clearance technique in the Kimmelstiel Wilson syndrome. On the other hand, the renal thresholds to glucose tend to be high.

The method was also used on 5 arteriosclerotic diabetics.

<u>DIABETICS with ARTERIOSCLEROSIS</u>						
	<u>E. R.P.F.</u>	<u>G.F.R.</u>	<u>F.F.</u>	<u>Tmg</u>	<u>G.F.R.</u> <u>Tmg</u> r.	<u>Threshold</u>
	125	41.6	.33	62.1	.670	150
	108	24	.22	33.4	.728	137
	160	38	.23	60	.635	154
	381	91.6	.24	122	.750	131
	341	44.5	.13	62	.720	139
<u>Mean</u>	223	47.9	.23	67.9	.700	142
<u>S.D.</u>	+114	+23.9	+0.065	+37.2	+0.050	+13.6
<u>100 X S.D.</u> <u>Mean</u>	51.2	50.8	27.3	46.5	7.1	9.5

Table 18.

These results were unexpected. There was even more reduction in essential renal plasma flow, and glomerular filtration rate than in the Kimmelstiel Wilson syndrome. The most striking difference between the two series lay in the much more evident

reduction of Tmg in the arteriosclerotic group. As a result the calculated thresholds of the arteriosclerotic group were below the range of calculated threshold of normal diabetics. This accorded with the clinical impression of the cases. It is perhaps important to note that these were cases in which arteriosclerosis had proceeded to such an extent that constant albuminuria was present, and three of the 5 have since died within a few months of the observations.

We concluded that the advanced arteriosclerotic kidneys show a more severe and more generalised reduction in function than the Kimmelstiel Wilson cases, and that a reduction in Tmg and lowered threshold might serve to distinguish the advanced arteriosclerotic diabetic from the Kimmelstiel Wilson syndrome.

The one case of chronic glomerulonephritis was studied and showed figures which were remarkably reduced, and at the same time showed a similar pattern to the mean of the Kimmelstiel Wilson cases.

	E.R.P.F.	GFR	FF	Tmg	$\frac{GFR}{Tmg}$	Thresh-
						hold
Chronic Glomerulonephritis	106	33.6	.30	87	.386	258
Mean of Kimmelstiel Wilson Syndromes	303	72	.25	202	.395	264

It will be observed that the $\frac{GFR}{Tmg}$ ratio and thresholds are very similar. Corcoran, Taylor &

Page (1948) in 6 patients said to have Kimmelstiel Wilson syndrome, found that their pattern was similar to that in glomerulonephritis. They do not note the evidence on which the diagnosis was based.

A comparison of the Glomerular Filtration Rates, Tmg's and Thresholds of the three main series was then studied.

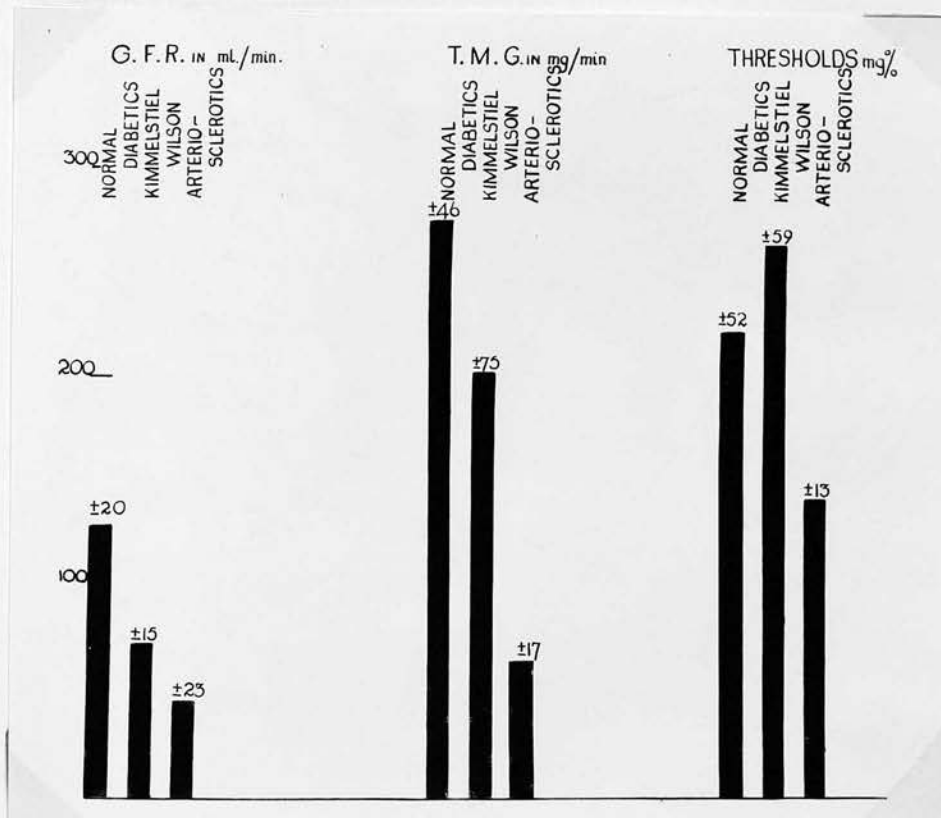


Table 19.

From this it will be seen that the glomerular Filtration Rate is normal in normal diabetics and progressively reduced in Kimmelstiel Wilson cases and in the arteriosclerotic. The Tmg is similarly progressively reduced but the reduction of Tmg in the Kimmelstiel Wilson syndrome is relatively much less

than that in the arteriosclerotic.

This observation would be in line with the pathological appearances. In the Kimmelstiel Wilson syndrome, the pathological process is one in which the maximum damage appears to fall upon the glomerulus. In the arteriosclerotic, the damage is more generally widespread and affects the tubules more equally.

The effect upon the calculated threshold would be that the Kimmelstiel Wilson's thresholds would tend to rise, the advanced arteriosclerotics tend to fall. Both observations of rising and falling renal thresholds in the elderly are clinically familiar. But the rising threshold of the Kimmelstiel Wilson syndrome might proceed to such an extent that the patients would be aglycosuric. Mirsky & Nelson report having encountered such patients. This effect may explain why some patients are not diagnosed as suffering from diabetes without special glucose tolerance tests, and may even account for a certain number reaching autopsy without having been known to be diabetic. (Page 32 of thesis).

The thresholds of the arteriosclerotic group are clearly pathological and fall without the normal range. The mean thresholds of the Kimmelstiel Wilson group, on the other hand, falls in the upper ranges of normal diabetics. It may also be that they are diabetics who have a high threshold and are therefore

more liable to develop Kimmelstiel Wilson lesions.

In the Kimmelstiel Wilson group, the thresholds are very variable. Of the three cases with the lowest thresholds, one was admittedly under very poor control, whilst another was not discovered to be diabetic until the full syndrome had developed, and therefore could have had no control until that moment. In the others, whose thresholds are high, an entirely false sense of the adequacy of control would be arrived at if the control were based upon examinations of the urine for sugar as it was in their cases. Thus, another interpretation of these findings would be that inadequate control of diabetes is a factor in the production or aggravation of the degenerative complications of diabetes, the full picture of which is seen in the Kimmelstiel Wilson Syndrome.

SUMMARY of THESIS

1) A study was made of the renal pathology of 43 consecutive diabetic autopsies, and the pathology grouped under five headings, separating those cases who showed Kimmelstiel Wilson lesions (11) from the other groups, the Arteriosclerotic (4), Arteriolo-sclerotic (3), Pyelonephritis (4) and "other diabetic" group (21).

A comparison of the clinical syndrome revealed that the Kimmelstiel Wilson lesions occur principally in elderly females, who show albuminuria and often renal infection. The lesion was characterised by the presence of

Hypertension with heart failure,

Oedema at least of the dependent parts,

Peripheral neuropathy,

Diabetic retinopathy where the fundus is not
obscured by cataract.

This syndrome was not found together in any of the other groups. The literature was discussed on these points.

2) A further series of observations were then made on 9 patients who exhibited the syndrome outlined. They showed that while the syndrome could be discovered for the first time in its fully developed state (3 cases) that the march of progress shown by the other six cases showed that, while eye changes,

oedema and peripheral neuropathy were early signs, hypertension developed later and progressed to failure if the disease was not terminated by one of the other hazards. Two cases coming to post mortem confirmed the clinical diagnosis.

3) A study of ancillary methods of diagnosis showed that the presence of doubly refractile bodies in the urine was a useful point of differential diagnosis from all but the nephrotic stage of chronic glomerulonephritis, whilst that condition might be distinguished by repeated Addis counts. The massive degree of albuminuria was found to be a useful point in the fully developed syndromes, but not of clear differential diagnostic value, and liable to extra-renal variations.

4) A study of renal clearances was made on normal diabetics (13), advanced arteriosclerotics (5), those with Kimmelstiel Wilson syndromes (7), and 1 case of chronic glomerulonephritis. The technique developed is described.

These studies showed that the normal diabetic had no demonstrable alteration in renal function. The Kimmelstiel Wilson cases had a considerably reduced function, the glomerular filtration rate being more reduced than the tubular maximum capacity for reabsorption of glucose, with the

result that the renal thresholds tended to be high. The advanced arteriosclerotic cases had a more severe and more generalised disturbance of function with the result that their thresholds were low. The suggestion is made that the raised thresholds in Kimmelstiel Wilson syndromes may explain the delay in diagnosing the diabetes which is encountered, or even some of the cases which show the lesions at autopsy but were not known to be diabetic in life. The suggestion is also made that the high thresholds may lead to inadequate control if urine estimations only are used, and that this may be at least an aggravating factor in the production of the full degenerative picture of the Kimmelstiel Wilson Syndrome.

My thanks are due particularly to Professor John McMichael for giving facilities to carry out this work in his department of medicine of the Post Graduate Medical School, Hammersmith, to Dr. Ian Doniach for his assistance with the pathological preparations, to Dr. Russell Fraser for access to the clinical material, and to Miss Evans, B.Sc., for her assistance in carrying out the chemical analyses.

BIBLIOGRAPHY.

- Addis, T. (1948) "Glomerular Nephritis".
The Macmillan Company.
New York.
- Ashton, N. (1949) Brit. J. Ophthal. 408.
- Bahr von, G. (1947) Acta med. scand.
Suppl. 196, p. 24.
- Baldwin, A.D. &
Root, H.F. (1940) New Engl. J. Med. 223. 244.
- Ballantyne, A.J. (1946) (Doyme Memorial Lecture)
Trans. Ophthal. Soc. U.K.
- Bell, E.T. (1942) Amer. J. Path. 18. 744.
- Bell, E.T. (1946) "Renal Diseases".
Kimpton, London.
- Corcoran, A.C.,
Taylor, R.D. &
Page, I.H. (1948) Ann. intern. med. 28. 560.
- Croom, J.H. &
Scott, G.I. (1949) Lancet. i: 555.
- Davson, J. &
Langley, F.A. (1944) J. Path. Bact. 56. 327.
- Derow, H.A.,
Altschule, M.D. &
Slesinger, M.J. (1939) New Engl. J. Med. 221. 1012.
- Dolger, J. (1946) Bull. N.Y. Acad. Med.
22. 482.
- Edmondson, H.A.,
Martin, H.E. &
Evans, N. (1947) Arch intern. Med. 79.
148.
- Ekehorn, G. (1946) Acta. med. scand. 125. 148.
- Friedenwald, T.S. (1948) Trans. Amer. Acad. Ophthal.
53, 73.
- Gauld, W.R.,
Stalker, A.L. &
Lyall, A. (1948) Brit. med. J. 2. 194.
- Goldring, W. &
Chasis, H. (1944) "Hypertension and Hyper-
tensive disease". New
York, The Commonwealth
fund.

- Goldring, W.,
Chasis, H.,
Ranges, H.A. &
Smith, H.W. (1940) J.clin.Invest. 19. 739.
- Goodof, I.I. (1945) Ann.intern.Med. 22. 373.
- Harrison, J.H. &
Bailey, O.T. (1942) J.Amer.med.Ass. 118.
15-20.
- Henderson, L.L.,
Spragle, R.G. &
Wagener, H.P. (1947) Amer.J.Med. 3. 131.
- Herbut, P.A. (1941) Arch. Path. 31. 501.
- Hogeman, O. (1948) Acta.med.scand. Supp.
CCXVI(216b).
- Horn, R.C. & Smetana, H. (1942) Amer.J.Path. 18. 93.
- Jordan, W.R. (1936) Arch.intern.Med. 57,
307-366.
- Joslin, E.P. (1946) "Treatment of Diabetes
Mellitus". London.
H.Kimpton. 8th edition.
- Kimmelstiel, P. &
Wilson, C. (1936) Amer.J.Path. 12. 83.
- Kimmelstiel, P., &
Porter, W.B. (1948) New Engl.J.Med. 238. 876.
and 238. 908.
- King & Garner. (1947) J.Clin.Path. 1. 30.
- King & Haselwood. (1948) "Micromethods in Medical
Biochemistry". E.T.King.
London.
- Laipply, T.C.,
Eitzen, O. &
Dutra, F.R. (1944) Arch intern.Med. 74. 354.
- Mann, G.V.,
Gardner, C. &
Root, H.F. (1949) Amer.J.Med. VII. 3.
- Marble, A. (1932) Amer.J.med.Sci. 183. 811.
- Mauser, C.L.,
Rowe, A.H. &
Michael, P.P.E. (1942) Ann.intern.Med. 17. 101.

- Millard, E.B. & Root, H.F. (1948) Amer. J. digest. Dis. 15, 41-51.
- Mirsky, I.A. & Nelson, N. (1943) Arch. intern. Med. 71. 827.
- Newburger, R.A. & Peters, J.P. (1939) Arch. intern. Med. 64. 1252.
- Newman, E.V., Gilman, A. & Phillips, F.S. (1946) Bull. Johns Hopk. Hosp. 79. 229.
- Nielsen, A. (1948) Acta med. scand. 130. 219-231.
- Porter, W.B. & Walker, H. (1941) J. Amer. med. Ass. 116. 459.
- Rifkin, H., Parker, J.G., Polin, E.B., Backman, J.L. & Spiro, D. (1948) Medicine. 27. 429.
- Robbins, S.L., Mallory, G.K. & Kinney, T.D. (1946) New Engl. J. Med. 235. 885.
- Robbins, S.L. & Tucker, A.W. (1944) New Engl. J. Med. 231. 865.
- Root, H.F. & Sharkey, T.P. (1936) Ann intern. Med. 9. 873.
- Rundles, R.W. (1945) Medicine Vol. 24, 111.
- Shannon, J.A., Farber, S. & Troast, L. (1941) Amer. J. Physiol. 133. 752.
- Shannon, J.A. & Fisher, S. (1938) Amer. J. Physiol. 122. 765.
- Siegal, S. (1940) J. Mt. Sinai Hosp. 6. 264.
- Siegal, S. & Allen, A.C. (1941) Amer. J. med. Sci. 201. 516.
- Smith, H.W. (1941) J. clin. Invest. 20. 631.
- Smith, H.W. (1943) J. Mt. Sinai Hosp. 10. 59.

Spühler, O. und
Zollinger, H.U.

(1943) Dtsch.Arch.Klin.Med.
190. 321.

Treusch, J.V.

(1945) Proc.Mayo Clin. 20. 393.

Wagener, H.P.,
Dry, T.J. &
Wilder, R.M.

(1934) New Engl.J.Med. 211.
1131.

Woltman, H.W. &
Wilder, R.M.

(1929) Arch.intern.Med. 44. 576.

APPENDIX "A"

Case Histories of Pathological Material.

Kimmelsteil Wilson Series (No.)	P.M. No.	No. Case	
1.	2861	39800	L.K.
2.	2090	11941	P.McK.
3.	4030	75208	S.S.
4.	2499	28004	E.P.
5.	3858	26597	F.H.
6.	3895	72144	S.W.
7.	1763	6385	R.H.
8.	3913	19410	E.B.
9.	4009	38195	E.S.
10.	2853	39739	L.O.
11.	4350	57190	E.E.
Arteriosclerosis Series (No.)	P.M. No.	No. Case	
12.	435	4115	E.H.
13.	914	3988	T.B.
14.	2810	36942	S.W.
15.	1119	none.	E.K.

Arteriolosclerosis Series (No.)	P.M. No.	No. Case	
16.	3153	49396	W.R.
17.	3448	16292	P.L.
18.	2928	2726	A.H.
Pyelonephritis Series (No.)	P.M. No.	No. Case	
19.	1654	8703	W.S.
20.	2186	15941	G.B.
21.	3045	45551	J.W.
22.	4129	76066	K.L.

SUMMARY of Cases with relevant signs, symptoms and pathological findings.

CASES OF KIMMELSTEIL WILSON GROUP.

Case 1. 39800.

A woman of normal build aged 81.

She was admitted with a request for paracentesis abdominis, as she was grossly oedematous. The oedema involved all her limbs, her face and her eyelids. She had an effusion of the right base and ascites. The oedema had steadily progressed over the last 11 months.

Her urine contained 280 mgs.% albumen. Microscopically there were some pus cells, epithelial cells and some red blood corpuscles. Her blood urea was 70 mgs.% and rose to 80. Her total proteins at first were 5.4 with an albumen/globulin ratio of .9. They fell to 4.4 total and A/G ratio of .5. Her cholesterol was 171 mg. at the time of first A/G ratio.

Her blood pressure was 160/100 which fell to 130/60 and her pulse became irregular before death. Clinically it was thought that she had a cardiac enlargement though the apex beat was obscured by oedema. Ward X-ray showed no evident cardiac enlargement. Her J.V.P. was +3. She was cyanosed.

Her eye grounds showed extensive retinopathy of a diabetic type.

Previous History. She had been admitted $4\frac{1}{2}$ years previously on account of difficulty with vision and

cystitis. At that time she showed a marked degree of diabetic retinitis with macular exudates and haemorrhages. Her blood pressure was 160/85; her heart was clinically enlarged and there was a systolic murmur. E.C.G. showed left ventricular preponderance, and X-ray showed calcareous plaques in her aorta. She complained of shooting pains in her arm and "growing pains" in both the calves, but her reflexes were then present except her ankle jerks. Her urine contained albumen 1+ and on culture grew staph. aureus and Bact. Coli. She said that her feet had been swelling for three months. She had been a diabetic for 11 years. Her fasting sugar was 185. At home she was treated on diet only but in hospital on her first admission she had been given 20 units Z.P.I. It was thought at that time that she was "incapable of keeping to a diet". There was no family history of diabetes.

POST MORTEM. Urinary system. Both kidneys lay $2\frac{1}{2}$ ins. lower than normal, and were separated by that distance from the suprarenals. The renal arteries rose $\frac{1}{2}$ in. below their usual position and were longer than normal. They were atheromatous but quite patent. The renal pelves and ureters were normal. The kidneys showed a fine granular surface. The capsule stripped easily. The cut surfaces were slightly red in the cortex with some slight obliteration of the demarcation area. They were firm and pink and might have passed for a straight forward

arteriosclerotic change. The bladder was small and showed a mild cystitis.

Microscopically. There was patchy ischaemic sclerosis and elastic hyperplasia of the large and medium-sized arterioles. The most striking changes were widespread areas of hyalinisation in the glomerular tufts and afferent arterioles. There was a minimum of fatty change.

Cardiovascular System: The heart weighed 420 gms. There was definite left ventricular enlargement and hypertrophy and moderate right ventricular hypertrophy with dilatation. The myocardium was dark and firm and had a stringy texture. Valves normal. The coronaries were severely atheromatous as was the aorta and its branches. The visceral arteries in general showed sclerosis.

Case 2. 11941.

An obese woman of 57.

She was admitted with generalised anasarca.

Her legs, abdomen, genitals, face and hands were all oedematous. She showed albuminuria ++, a few granular casts, sugar ++, a trace of acetone. Catheter specimen showed a growth of B. Coli and B. Proteus on culture, though no pus was seen in the deposit. Sugar-free samples of urine had a fixed specific gravity of 1010. Pyelogram showed some excretion on the right, but not appreciable

excretion on the left. Her urea clearance test averaged 31% of normal. Her blood pressure was 180/100. Her vessels were thickened, her heart enlarged. There was an apical systolic murmur and the aortic second sound was accentuated. X-ray showed cardiac enlargement in the transverse diameter, and E.C.G. showed left axis deviation. She showed some signs of failure. She was cyanosed. Her jugular venous pressure was 1 - 2 cms. above the sternal angle and she had crepitations at both bases. She gave a history of breathlessness on exertion for 2 - 3 years, three months occasional nocturnal paroxysmal dyspnoea, and retrosternal pain on exertion relieved by rest.

Her fundi showed haemorrhages and many exudates but no vein nippings. She complained of shooting pains down her legs and a feeling of uselessness occasioned especially by changes of temperature. There were no knee or ankle jerks elicited.

She finally became comatose and died with marked general anasarca.

Previous History. She gave a doubtful history of six weeks "kidney trouble" seventeen years previously. She said that she had difficulty in passing urine and that this was accompanied by menorrhagia lasting the whole six weeks. She had been diabetic for two years, treated for the first year with 30 units of insulin daily but diet only for the last year, which she found "difficult to keep to". There was no

diabetic family history.

POST MORTEM. Urinary System. The right kidney weighed 210 gms., the left 200. Both were large and oedematous. They were bright pink in colour with yellowish flecks in the cortical zone both on the cut and capsular surfaces. The capsule stripped easily leaving a surface exhibiting numerous depressed scarred areas over which there were local capsular adhesions. The cut surface showed some blurring of the cortico-medullary demarcation and of the mornal striation, and the cortex though apparently swollen and oedematous was reduced in amount. The smaller arteries in the boundary zone were prominent. The pelves, ureter and bladder were natural.

Microscopically. The glomeruli showed beautifully the changes described as intercapillary glomerulo-sclerosis. There were a number of hyaline caps.

Cardiovascular System. The heart weighed 300 gms. There was an excess of fluid in the pericardium. The heart did not appear to be enlarged but there was slight thickening of the wall of the left ventricle. The myocardium and valves were normal. The coronary arteries showed no gross changes. The aorta showed a fair amount of nodular atheroma but not complete loss of elasticity and no calcification.

Case 3. 75208.

An obese woman of 70.

She was admitted with severe hypoglycaemic coma from which she did not recover. Her sacrum and ankles were oedematous. She showed 1+ albumen and a catheter specimen contained a fair number of pus cells and grew coliform bacilli.

Her blood pressure was 180/60. Her jugular venous pressure was not raised but a history was obtained of nocturnal paroxysmal dyspnoea. Her fundi were not observed because there were bilateral cataracts. She had been blind for three years. She had complained of "pins and needles" and that her legs went "dead". Ankle jerks were not obtainable.

Previous History. There was no history of urinary trouble. She had been a diabetic for about 20 years.

According to her daughter, she had been admitted to various hospitals in either diabetic coma or hypoglycaemia some 15 to 20 times and that she had frequent severe headaches and attacks of giddiness. She had taken 20 units Z.P.I. daily and diet. Her fasting sugar was 172 mgs. Her aunt had died from diabetes. She herself had five children all alive and well.

POST MORTEM. Urinary System. The kidneys weighed 220 gms. The capsule was rather adherent to a finely granular surface. The cortex was 4-5 mms.

thick, the cortical pattern well preserved and the cortico-medullary junction clear. A number of small cysts were present. The total thickness of the kidney was reduced being replaced by an increased pelvic fat. The appearance on the whole suggested arteriosclerosis rather than nephritis. The pelves were healthy and free from any infection. The ureters were normal and no cystitis was seen.

Microscopically. The kidneys showed some focal arteriosclerotic atrophy and the glomeruli showed typical intercapillary glomerulosclerosis.

Cardiovascular System. The heart weighed 250 gms. and was neither dilated nor hypertrophied. The coronary vessels were remarkably free from atheroma in the right and left circumflex branches. The descending left branch however, was severely atheromatous with some calcification and apparent narrowing. The aorta showed scattered nodules of atheroma, some of those in the lower abdominal portion being calcified. The cerebral vessels were remarkably healthy only an occasional plaque of atheroma being visible.

Case 4. 28004.

A thin senile woman of 80 (who used to be very stout).

She was admitted with broncho-pneumonia, from which she died.

She showed 1+ of albumen and oedema of her legs. Her blood urea was 21 mgs.%, her cholesterol 220 mgs. and her total blood proteins 7.8 gms.

Her blood pressure at this stage was only 130/68 and there was a systolic murmur at all areas. Her haemoglobin was 83%. She gave a history of being easily short of breath. She showed thickening of her radial arteries. There was no pulse in her popliteal, posterior tibial or dorsalis pedis arteries. No abdominal or ankle jerks were obtained. She had a gangrenous big toe.

Previous History. There was no history of renal disease. She had been a diabetic for seven years, of a mild type, taking 10 units of insulin for the first five years and diet only since, which she had "not managed to keep to". She had been in the hospital seven years previously when the diagnosis of diabetes was established and was at that time considered to be suffering from essential hypertension and peripheral neuritis. Her fasting blood sugar was 240 mgs. She then had a blood pressure of 210/110. Her apex beat was in the 5th space just outside the midclavicular line. Her vessels were tortuous and her aortic second sound accentuated. Neither dorsalis pedis nor posterior tibial arteries were palpable, and her feet were anaesthetic to cotton wool and pin-prick. She had oedema of the sacrum and complained of occasional swelling of the feet for the last thirteen months. As she had been

dyspnoeic on exertion for this time, the oedema was considered to be cardiac in origin. She had been again in hospital six months before her final admission. Her blood pressure at that time was 210/100, she had pitting oedema of both feet and her liver was palpable two finger-breadths below the costal margin. Her right fundus could not be seen because of the cataract, but her left fundus showed many punctate haemorrhages. Because of a persistent albuminuria, a urea clearance test was done which showed 28% of average function. A significant note was then entered - "Note impaired kidney function and albuminuria, i.e. Kimmelsteil Wilson syndrome. Watch for development of more gross nephrosis".

POST MORTEM. Urinary System. Microscopically.

The kidneys show numerous scattered areas of hyaline in the glomeruli. Some show fibrous thickening of Bowman's capsule, some are hypertrophic and others atrophic. There are small wedge-shaped areas of atrophic tubules with increased fibrous interstitial tissue and lymphocytic infiltration. The afferent arterioles show hyaline thickening - small and medium-sized vessels show elastic hyperplasia. There is interstitial fibrosis of the medulla. Fat has been deposited chiefly in the collecting tubules and loops of Henle.

Cardiovascular System. The aorta showed extensive atheroma with calcification, ulceration and recent intimal haemorrhages and surface thrombosis. There was generalised arteriosclerosis.

Case 5. 26597.

An obese woman of 62.

She was admitted in coma from which she died in ten days.

She showed a heavy albuminuria, her blood urea was 250 mgs.% and a urinary culture grew B. Coli.

Her blood pressure was 150/80; she showed no cardiac enlargement clinically. Her liver was tender to two finger breadths below the costal margin. Her haemoglobin was 77%.

Her fundi showed extensive diabetic retinitis in the right eye, the left was not seen because of cataract.

No abdominal or ankle jerks were obtained.

Her blood sugar on admission was 624 mgs.%.

Previous History. She had no history of nephritis. She had been admitted for diabetes and cataract four years previously when albuminuria was noted, as was the presence of an urinary infection. She refused tablets for treatment of this infection. At that time she also had oedema of the ankles and although both dorsalis pedis arteries were felt, ankle jerks were not obtained and there were subjective pains in

the knees and ankles. She was practically blind with bilateral cataract. Her blood pressure was 135/90, but when seen in Out-Patients 10 months before this B.P. was 180/110. She had been diabetic for at least 6 years. Her diabetes was controlled with 25 Z.P.I. and 30 soluble. She had a family history of diabetes.

POST MORTEM. Urinary System. The kidneys were greatly enlarged. The right weighed 330 gms. and the left 260. Both showed superficially irregular wide areas of pseudo-lobulation, the capsule stripped easily leaving a smooth surface. On section, the right kidney showed a pyonephrosis and a grey-brown hard mulberry-like calculus measuring $3/8$ ins. in diameter was present in the calix second from the top. The pelvis was filled with purulent urine and the part of the pelvis which lined the papillae formed a well-defined white inflammatory zone. A white line also separated the papillae from the rest of the kidney giving the appearance of necrosis of the papillae separated from the rest by a reacting zone. The cortex and medulla were paler than their corresponding components of the left kidney but the line of demarcation between the cortex and the medulla was distinct. The cortex shows white lines passing radially suggesting extension of the infection into the kidney with the production of a pyelonephritis. Abscesses however, were not present. The left kidney showed a relative normal pattern naked eye.

The ureters were not dilated. The right ureter contained purulent urine, as did the bladder which showed no abnormality in its wall.

Microscopically. Left Kidney. The capsule is of normal thickness and only slightly infiltrated with inflammatory cells. The glomeruli are all abnormal and demonstrate all stages of intercapillary hyalinisation. The earliest lesion appears as an enlargement of the glomerulus with one or two rounded areas of intercapillary hyalinisation. These lesions are associated with a hyalinisation of the basement membrane of Bowman's capsule. The tubules are healthy. The interstitial connecting tissue shows lymphocytic and plasmacell infiltrations in areas where the glomeruli are completely destroyed. In addition there is an accompanying polymorph infiltration in one or two areas but this is insignificant as compared with that seen in the right kidney. The main arteries show relatively little abnormality.

Right Kidney. The capsule is moderately thickened and shows areas of haemorrhage and fibrin exudate. It is infiltrated from the underlying renal interstitial tissue by lymphocytes, plasmacells and polymorphs, and some areas show fibroblast proliferation with the formation of new vessels. The glomeruli demonstrate the same intercapillary lesion as the opposite kidney - the lesions being somewhat more advanced. The tubules have similar thickening of

the basement membrane in some areas. They show in addition various grades of degeneration of the tubular epithelium associated with the surrounding inflammatory reaction of the interstitial tissues. A number of collecting tubules in the medulla especially in the surviving portion of the renal papillae, contain polymorphs in the lumen. The interstitial connective tissue is almost diffusely infiltrated with inflammatory cells consisting of plasmacells, newly formed fibroblasts, lymphocytes and polymorphs suggesting an acute process superimposed on the chronic inflammatory reaction which was also observed in the opposite kidney. The polymorph reaction becomes more marked as one moves towards the pelvis. The pelvis itself is destroyed and consists of a mass of debris and degenerating polymorphs, and there is an underlying chronic reaction in which there are remains of the renal and pelvic fat. In certain areas, however, the polymorphs have infiltrated beyond the pelvis into the interstitial tissue of the renal papillae to invade the kidney substance in varying degree, resulting in an acute pyelonephritis with some areas of small abscess formation. In various papillae there are large areas of necrosis surrounded by a zone of inflammatory cells - the whole structure resembling an infarct. These lesions appear to be those described as "papillitis renis necroticans".

Cardiovascular System. The heart weighed 370 gms. The left ventricle was hypertrophied and section of the muscle especially in the interventricular septum showed fine white pin-point areas of seeming fibrosis. The aorta showed slight atheroma at its commencement and along the arch. This became more marked in the descending aorta especially in the abdominal portion. The openings of the coronary vessels were surrounded by atheroma, and the vessels themselves showed a severe degree of atheroma out of all proportion to that found in the arch. Calcification had occurred resulting in narrow tortuous pipe-stem vessels. The changes were more marked in the left branch. There was no evidence of recent thrombus or complete occlusion of the main branches as far as they could be traced. The basilar were narrow and showed slight atheromatous change.

Case 6. 72144.

An obese woman of 67.

She was admitted with a broncho-pneumonia from which she died in 24 hours.

She showed a heavy albuminuria and her urine showed granular casts with occasional red blood cells. She had gross pitting oedema of her limbs, her trunk up to the tenth thoracic vertebra and both forearms. She had ascites and an effusion at the left base. The swelling of the legs had been present for one month.

Her blood pressure was 202/118. Her apex beat was 7 ins. from the mid-line and forceful in character. There was a gallop rhythm. Her jugular venous pressure was +5 above the sternal angle. She was dyspnoeic and cyanosed. She had been unable to lie flat for one month. There were crepitations at the right base. She had bilateral cataracts but the left fundus was seen to contain both haemorrhages and exudates.

Previous History. She had an attack one year previously of breathlessness with swelling of the legs. Five months previously she had been in another hospital for nine weeks with "congestive cardiac failure". She had no history of renal disease. She had been a diabetic for three years, discovered on account of her cataracts. She had 20 units Z.P.I. until three months before admission when she was treated with diet only. There was no family history of diabetes. She had had chronic bronchitis for the last three winters.

POST MORTEM. Urinary System. The right kidney weighed 160 and the left 170 gms. The capsule stripped easily leaving a finely granular surface. The cut surface showed an excellent pattern exaggerated by congestion. The ureters and bladder were normal.

Microscopically. There were arteriosclerotic changes of moderate severity. Occasional glomeruli showed one or two hyaline spheres of intercapillary glomerulosclerosis.

Cardiovascular System. Her heart weighed 450 gms. The left ventricle was slightly hypertrophied, but definitely dilated. The muscles of the left ventricle showed fibrous streaking and the scar of an old infarct at the apex. The right ventricle was markedly hypertrophied and dilated. Both main coronaries and their branches showed severe calcareous atheroma and a partial stenosis. The aorta and branches showed severe calcified atheroma. The proximal 4 cms. of each cerebral artery was also severely atheromatous.

Case 7. 6385.

A man of 74 of thin build.

He was admitted complaining of swelling of the legs, arms and abdomen and shortness of breath, and died in a few days with generalised anasarca.

His urine had albumen ++. His total proteins were 6.4 gm.

His blood pressure was 160/90. His haemoglobin was 54%. He was orthopnoeic, pale, with slight cyanosis. His heart was $5\frac{1}{2}$ " from the middle line. There were no murmurs, but a gallop rhythm. X-ray showed gross enlargement of all chambers and bilateral pleural effusion. E.C.G. showed left axis deviation and low voltage. He was breathless on the slightest exertion. His jugular venous pressure up to the angle of the jaw. There

were moist sounds in both lungs, in addition to the pleural effusion. His liver was 4 ins. below the costal margin and there was gross ascites and gross sacral oedema. No knee or ankle jerks obtained.

Previous History. He had been in the hospital previously for 7 months a year and a half before his final admission. At that time, he had oedema of the ankles during his whole stay which at times reached up to his thighs and sacrum. His blood pressure was 185/90. His left ventricle was grossly enlarged and the E.C.G. showed left axis deviation with the following comment - "The absence of abnormalities other than axis deviation is unusual in cases of left ventricular failure from any cause". He had an infected toe and complained of shooting pains in the legs. His abdominal jerks were absent as were his ankle jerks, and he had loss of vibration sense below the knees and some loss of sensation so that his toe was opened without even a local anaesthetic. Both calves were tender. His anterior and posterior tibial and dorsalis pedis arteries were palpable. Both eyes showed early lens opacities. His urine though showing no albumen on admission showed 1+ albumen thereafter. There were pus cells and a few red blood cells, and culture grew staph aureus. This urinary infection was unresponsive to treatment. His blood urea was 58 mgs.% and remained raised. On discharge, the

following remark was made - "Throughout his stay in hospital his blood urea has been slightly raised and there is no doubt he has some arteriosclerotic changes in his kidney". He had been diabetic for two and a half years, treated with diet and 40 units Z.P.I. His fasting sugar was 289 mgs.%. His father had died of diabetic gangrene. He had no other evidence of previous renal disease.

POST MORTEM. Urinary System. Right kidney weighed 120 gms., the left 140. They were rather swollen. The capsules were slightly adherent and the glomeruli prominent. Bladder normal.

Microscopically. There was a marked cortical atrophy with numerous areas of discrete hyalinisation in the glomeruli. There were many areas of tubular atrophy and a general increase in interstitial connective tissue but little fatty change. The medium-sized vessels showed marked sclerosis, thickening of the intima and multiplication of the elastic lamina.

Cardiovascular System. The heart weighed 375 gms. There was an excess of clear fluid in the pericardium. The heart itself was not greatly enlarged though there was some relative hypertrophy of the left ventricle. The coronary arteries showed marked atheroma and narrowing of all branches but nowhere complete occlusion. The aorta was inelastic and showed a moderate atheroma increasing in the descending aorta. There were no gross

changes or calcification. The iliac arteries were tortuous and fibrotic.

Case 8. 19410.

A woman of normal build aged 72, who had previously had one leg amputated for gangrene.

She was admitted in extreme degree of orthopnoea leading to death in two days.

Her urine showed a trace of albumen and her sacrum was oedematous. Her blood pressure was then only 120/80 although her apex beat was 6 ins. from the middle line in the fifth space. She was fibrillating, her jugular venous pressure was raised 2 cms. She was orthopnoeic and there were rales all over her chest. Her Hb. was 60%. Bilateral cataracts.

Previous History. She had been admitted six years previously for hypertension and five years previously on the surgical side for amputation of the right leg. On both of these admissions there were frequent traces of albumen. A urea clearance test on the first admission showed 75% of normal function. Centrifuged specimen of urine showed nothing abnormal. Her blood pressure at that time was 218/90 and she gave a history of dyspnoea for ten years. She required three pillows to sleep in bed. Her haemoglobin was 60%. There was slight "kinking" only in the fundi. She had no ankle jerks and great tenderness in the right calf. She had been

diabetic for 8 years controlled by diet and 5 - 10 units Z.P.I. Her fasting sugar was 200 mgs.%. There was no family history of diabetes.

POST MORTEM. Urinary System. Right kidney weighed 130 gms. and the left 140. Both showed a granular capsular surface with a tendency to adhesions, and a reduction of cortical substance, and were considered to be arteriosclerotic kidneys. The pelves, ureters and the bladder were natural.

Microscopically. There was patchy ischaemic atrophy. Occasional glomeruli show areas of intercapillary glomerulosclerosis. The afferent arterioles show hyaline fatty change. The medium arteries show elastic reduplication but intimal proliferation is strikingly little.

Cardiovascular System. The heart weighed 470 gms. There was a dense fibrous pericardial adhesion on the posterior wall of the left ventricle. The left ventricle was dilated and hypertrophied. In the posterior wall there was a healed myocardial infarction with fibrous replacement and great thinning of the wall. The other chambers of the heart were dilated. The coronary arteries were grossly atheromatous and tortuous. An old thrombus completely occluded the circumflex branch of the left coronary artery supplying the fibrosed area of myocardium. The aorta was atheromatous and calcified as were all the main arteries.

Case 9. 38196.

A woman of 80 who was admitted in an extreme degree of heart failure from which she died in two days.

Her urine showed albumen ++. Her blood urea was 29 mgs. She was oedematous to the knees and had some oedema of the sacrum. She was dyspnoeic and cyanosed, and her J.V.P. was + 10 cms. Her liver was enlarged 3 fingerbreadths. There was an effusion at one base and moist sounds in both lungs. Her blood pressure was indeterminable, and the heart size could not be estimated clinically. Her radial pulse was almost impalpable, and only the right femoral pulse was felt in the legs. There was intense peripheral cyanosis. She had complained of aching pains in the legs for some time. The ankle jerks could not be obtained, but no other nervous system abnormalities were noted. She had bilateral cataracts.

Previous History. She had been breathless on exertion for "some time". She had had occasional attacks of paroxysmal nocturnal dyspnoea. She had no history of previous renal trouble. When her diabetes had been diagnosed three years previously, she had a fasting sugar of 200 mgs. Clinically no cardiac enlargement was detected but she showed apparent left ventricular enlargement. B.P. 110/90. Her Hb. was 109%. She had been again in hospital ten months previously with a carbuncle, and had been

sufficiently controlled to go home on diet alone. At that time there was a trace of albumen in the urine. There was no family history of diabetes.

POST MORTEM. Urinary System. The right kidney weighed 140 gms. and the left 130. The outer surfaces showed coarse retracted scars. The cortex was a trifle reduced. The cortical pattern was imperfectly defined, though the corticomedullary junction was clear. The appearance suggested focal arteriosclerotic atrophy or healed pyelonephritis. Ureters and bladder were healthy.

Microscopically. The vessels show diffuse sclerosis. The arterioles are frequently hyaline. There are foci of ischaemic atrophy, occasional glomeruli show intercapillary glomerulosclerosis.

Cardiovascular System. The pericardium contained 50 ccs. of clear fluid. There was moderate dilatation of the right side. There was a healed myocardial infarct at the apex of the left ventricle anteriorly. There was a little thrombus over this. The infarct is about 3 cms. at its widest. There is another healed infarct at the base posteriorly about 2 cms. at its widest. No recent infarct could be seen and the muscles appeared healthy apart from the infarcts.

Coronary arteries. The descending left branch was rigid and calcified and its lumen narrowed to about 1 mm. The main right coronary was narrowed at its mouth by aortic atheroma and there was a recent

purple thrombus at the level of the aortic mouth. The aorta showed moderately severe nodular atheroma in the upper half and severe confluent calcareous atheroma in the lower half. All the major peripheral arteries showed calcareous atheroma of a severe degree.

Case 10. 39737.

A woman of 52 who was admitted comatose, dry tongue, flaccid limbs and cold extremities and died 25 hours after admission. In view of her condition and rapid termination adequate clinical notes are not available. She had an albuminuria of 30 mgs.%, and 1,600 mgs.% of sugar in the urine. Abdominal and ankle jerks absent, doubtful knee jerks. Her blood sugar was at one time 653 mgs.%. Her blood pressure was not determinable. She had an old mitral stenosis and died of suppurative bronchitis and bronchopneumonia.

POST MORTEM. Urinary System. Kidneys weighed 270 gms. The capsule stripped easily and there was no evident sclerosis. There was a good line of demarcation between the cortex and the medulla, but the cortex was definitely pale. The ureters and bladder were normal.

Microscopically. In addition to congestion and cloudy swelling there was a moderate degree of intercapillary glomerulosclerosis with hyaline patches in

several glomeruli.

Cardiovascular System. The heart weighed 240 gms. The mitral orifice barely admitted one finger and the cusps were fused and stenosed. The contact margins were covered with fine verrucose vegetation (rheumatic in appearance) and one large firm pale vegetation 0.5 cms. across (bacterial endocarditis in appearance). The left ventricle was small and the muscle firm and brown. The coronaries were smooth and patent. The aorta and branches were fairly free from atheroma.

Case 11. 57190.

An obese woman brought to hospital unconscious as a result of a cerebral haemorrhage from which she succumbed.

She presented then typical signs of a right-sided hemiplegia. Her heart was enlarged. Blood pressure 210/120. Gross haemorrhages and exudates in both retinae, of a diabetic type.

Blood sugar was 208 mgs.%. C.S.U. granular casts, red cells and pus cells. Albumen +++.

Coma gradually deepened until she died.

She had been losing weight for 5 months. She had been previously in hospital 18 months before when the diabetes was discovered. She was admitted because of an infected abscess on the dorsum of the foot. No thirst or polyuria. B.P.195/95.

Numerous small round haemorrhages and clear white exudates especially at the macula. X-ray LV+.

E.C.G. LV++. Hb. 93%. Auricular fibrillation.

Slight oedema of the ankles. Knee jerks only present with reinforcement. No ankle jerks. All vessels palpable. Heavy albuminuria and B.Coli or C.S.U. Urea clearance 43.3%. "Mirsky" threshold 300 mgs.%. G.T.C. 322 - 338 - 420 - 440 - 462. Stabilised on diet only. Discharged without insulin.

POST MORTEM. Urinary System. Kidneys together weighed 400 gms. Capsule stripped readily from a coarsely granular surface. Section shows a pale cortex of average thickness with indistinct markings and enlarged pale glomeruli. The boundary zone is fairly distinct. Boundary vessels very prominent and often almost completely obstructed by atheromatous cushions. Pelves normal - ureters sound. Bladder wall congested.

Microscopically. A Kimmelsteil Wilson lesion with singularly beautiful glomerular lesions. Nearly every glomerulus shows a thickened basement membrane and most a thickened capsule. Balls of collagen staining material lying in the centre of the loops are frequent. A fair number of glomeruli are completely hyalinised. Changes in the rest of the kidney are relatively slight.

Cardiovascular System. The heart weighs 600 gms. with a gross excess of epicardial fat but only moderate fatty infiltration. Valves normal. Right side moderately dilated. Right ventricle 0.5 mms. thick. Left ventricle 2.0 mms. thick. Muscle firm and pale. Coronaries show many smooth cushions of atheroma. Aorta showed marked atheroma. Renal arteries clear.

CASES OF ARTERIOSCLEROTIC GROUP.

Case 12. 4115.

A woman of 75 who was admitted in heart failure.

She showed 1+ of albumen and a blood urea of 30 mg%. She had no oedema. Her blood pressure was 135/70 on admission but the heart rate was 120 and there was a tick-tack rhythm. Her heart was not clinically enlarged. Her liver was palpable one inch below the costal margin. Her radial arteries were palpable and tortuous. Her dorsalis pedis was palpable but the posterior tibial was not palpable on the left side. Her eye grounds showed no haemorrhage or exudate. She complained of occasional tinglings in the legs and neither knee nor ankle jerks could be obtained. She had attended the Out-Patients 3 months previously when her blood pressure was noted to be 160/110 and she had slight cyanosis. She then had a history of diabetes for 3 years and had been put on 5 units insulin night and morning. There was no previous history of nephritis.

Post Mortem. Urinary system. Each kidney weighed 170 gms. The capsules were slightly thickened but stripped fairly easily leaving an outer surface with a few irregular depressions and a number of cysts up to about $\frac{1}{3}$ in. in diameter. The cut surface showed slight narrowing of the cortex, a vascular pattern which was fairly regular and a distinct cortico-medullary junction. There was some thickening of the vessels. The pelvis and ureters were healthy. The

left kidney showed rather more numerous cysts and some deeper irregular depressions.

Microscopically. There is sclerosis of the arteries and foci of ischaemic fibrosis under the capsule.

There are some cystic tubules and rather numerous polymorphs in the glomeruli. There is considerable degenerative swelling of the tubular cells in the cortex but very little fat.

Cardiovascular system. There was a fibro-purulent pericarditis with shaggy yellow fibrous exudate on all surfaces and the pericardium was considerably distended by rather watery pus. The exudate was beginning to be quite densely adherent to the membrane and the inflammation had apparently been present about one week. There was slight right ventricular hypertrophy. The left auricle and ventricle were thin-walled. The heart muscle was brown and apparently of rather poor quality. The branches of the coronary artery showed some atheroma but there was no fibrous change in the heart muscle. The aorta showed fairly severe atheroma becoming worse towards its lower end. The common iliacs were arteriosclerotic and greatly dilated.

Case 13. 3988.

A stout man of 77 who was admitted with gangrene of one foot, and died suddenly while awaiting operation.

His urine showed albumen 1+ and there was a period of unexplained haematuria in the ward. He had no oedema. His blood pressure was 160/85. Neither the dorsalis pedis nor the posterior tibial artery could be felt in the left leg which was the seat of gangrene.

He had been in hospital two and a half years previously when his blood pressure was 200/100, and there was thought to be slight cardiac enlargement. At that time he complained of being short of breath on climbing stairs. It was then noted that he had "no evidence of peripheral neuritis". He had been a known diabetic for 4 years, of a mild type not requiring insulin. There was a family history of diabetes.

Post Mortem. Urinary system. Each kidney weighed 220 gms. The surface showed generalised granularity. The cut surface was congested but otherwise normal. The ureters were normal. The bladder showed a cystitis. It was full of pus and mucus and the mucosa was intensely congested.

Microscopically. The kidneys show a little patchy arteriosclerotic atrophy.

Cardiovascular system. The heart weighed 390 gms. There was a moderate dilatation of the right side. The aortic valves showed slight calcification at the bases. The muscle was distinctly flabby but showed no evidence of infarct or fibrosis. The coronary arteries showed fairly severe atheroma, particularly in the descending left branch. There was no

occlusion, old or recent. The aorta showed severe ulcerative atheroma throughout. There was very little calcification. The left popliteal and posterior tibial arteries showed moderate atheroma but had good-sized lumens.

Case 14. 36942.

A stout man of 64 who was admitted as a result of an accident and died suddenly from massive pulmonary embolism.

His urine showed varying amounts of albumen; from a trace to 1+. Culture showed a growth of B. Coli and Staph. Aureus, although there were only a few pus cells. He also had a sharp haematuria in the ward of unexplained origin. His blood urea was 62mgs%. His blood pressure was 200/95, and his heart was considered clinically within normal limits. He had no evidence of heart failure or of oedema. He had a hemiplegia which was thought to have been due to a vascular accident, but which was discovered at post mortem to be due to a glioma. His diabetes was only diagnosed one month before death. He had a fasting sugar of 189 mgs%, and needed 15 units of soluble insulin night and morning during his stay. There was no family history of diabetes.

Post Mortem. Urinary system. The kidneys together weighed 470 gms. They were congested and showed moderate arteriosclerosis. Ureters and bladder normal.

Microscopically. Moderate arteriosclerosis and ischaemia only.

Cardiovascular system. The heart weighed 430 gms. The left ventricle was hypertrophied and dilated and showed slight fibrosis of the papillary muscles. There was slight hypertrophy of the right ventricle. The coronaries were atheromatous but patent. The aorta and branches showed moderately severe atheroma. The left femoral vein was occluded by an antemortem clot which extended into the profunda.

Case 15. (None).

A stout woman of 60 who was admitted deeply comatose and moribund after an illness outside lasting about 10 days. She had well-marked air hunger and had lost her corneal reflex. She had a large fluctuating abscess of the thigh. As she died in little over two hours after admission there were no adequate notes on her clinical condition. Her urine was loaded with sugar and acetone. She was not a known diabetic but her husband said he had noticed that she had been drinking a lot lately and had lost some weight.

Post Mortem. Urinary system. The right kidney weighed 225 gms, the left 190. Both appeared swollen and rather pale and soft. The ureter and bladder were normal.

Microscopically. There is marked swelling of the tubular epithelium and occasional thickening of the vessels. There are fibrous patches and an occasional completely hyaline glomerulus.

Cardiovascular System. The heart weighed 460 gms. There was some dilatation of all chambers. The muscle was soft and flabby. The valves and endocardium showed some haemoglobin staining. The coronary arteries showed only some slight atheroma. The aorta showed a few nodules of atheroma.

CASES OF ARTERIOLOSCLEROTIC GROUP.

Case 16.

A stout woman of 41, admitted in coma with well-marked air hunger, low ocular tension and inelastic skin. She died on the day of admission.

Her urine contained 812 mgs% albumen at this time. There was no oedema. Her blood pressure on admission was 130/90 but rapidly fell. Her blood sugar on admission was 495 mgs%. She had a carbuncle on the back of her neck.

She had been admitted to the wards six years previously with a pyelonephritis. She had a B. Coli. infection which responded to treatment. A retrograde pyelogram revealed no abnormality. On that admission her blood pressure was 140/85 and her Hb. 106%. She had not been known to be diabetic previous to her admission in coma, although she had complained of

thirst and polyuria for a "long time" and had lost weight.

Post Mortem. Urinary system. Each kidney weighed 240 gms. The right capsule stripped easily and the surface was smooth. The cut surface showed a widening of the cortex with normal vascular markings, and yellowish streaking extending into the medullary portion. The left showed similar changes. Ureter and bladder were normal.

Microscopically. The changes are characteristic of essential hypertension. There is well-marked fibrous tissue increase in the medulla.

Cardiovascular system. The heart weighed 310 gms. The right auricle showed some ballooning and was filled with post mortem clot. There was atheromatous thickening of the aortic cusps. The coronary vessels showed moderate atheroma. The aorta showed only slight atheroma of the abdominal part.

Case 17. 16292.

A woman of 42 brought in in the last stages of coma from which she died in a few hours.

She was an old case of diabetes, having been admitted once in coma eight years previously, and had two other admissions for stabilisation.

Eight years previously she had been noted to have oedema of the ankles, and a trace of albuminuria. Urine culture at that time grew B. Coli. Her blood

pressure was 158/82. There was no evidence of cardiac enlargement or heart failure. She had pains in the legs worse at night time and relieved by hanging out of bed. Her ankle jerks were not present. Her retinae showed no abnormality.

Three years before admission she was again in hospital in an effort to stabilise her diabetes. Her urine at this time contained 1+ of albumen and she had oedema of her legs which had been present for six months on admission. Her urine contained +++ bacteria but no pus and was sterilised with sulphapyridine. She was then weak from the knees down and had painful calves, though all vessels were palpable. Her blood pressure on this admission was 122/84. Her fundi showed no abnormality.

Her diabetes had always been difficult to stabilise. At one time three doses daily were tried and although the glycosuria was diminished, it was never properly stabilised. Her fasting sugar was 396. She was taking Z.P.I. 28 and soluble 20 at the time of her last admission. There was no family history of diabetes.

Post Mortem. Urinary system. The right kidney weighed 280 gms. It was enlarged, firm and the capsule stripped with the greatest ease, leaving a smooth surface covered with a honeycomb network of fine vessels. The cut surface showed a pale, yellowish cortex with the glomeruli standing out as congested shiny spots. The vessels of the pelvis

were also congested. The left kidney weighed 230 gms. and was similar to the right. The ureters were normal. The bladder contained a small amount of pusy urine and the mucosa was slightly injected.

Microscopically. Most glomeruli show fibrosis of a mild degree. There is some ischaemic thickening of Bowman's capsule in some places and hyalinisation of afferent arterioles. The epithelium lining the loops of Henle show marked basal vacuolation due probably to glycogen.

Cardiovascular System. There was a slight excess of free fluid in the peridardial sac. Weight 390 gms. A flabby heart with pale myocardium showing a few endocardial haemorrhages. There was moderate dilatation of both ventricles. Valves normal. Coronary arteries of good bore, showing only very mild atheromatous streaking. The aorta was normal apart from a slight atheromatous streaking. The branch vessels were normal.

Case 18. 2726.

A woman of normal build aged 73, who was admitted with an ulcer of one toe and died suddenly from coronary thrombosis.

Her urine contained varying amounts of albumen from a trace to ++ and there were epithelial casts and leucocytes. She had had swelling of both legs for three months. Her blood urea was 36 mgs%. Her

blood pressure was 138/90. Clinically her heart was enlarged being five inches from the mid-line in the fifth space. There was a systolic murmur at the apex. X-ray showed left ventricular hypertrophy and all chambers to be enlarged. E.C.G. showed a low voltage Q.R.S. complex and S.T. depressed in one and two and flat in three. Her J.V.P. was +4. There were basal crepitations, an effusion on the right side and her liver was two fingerbreadths enlarged. Her haemoglobin was 66%. She gave a history of 3 - 4 months breathlessness on exertion and had had occasional nocturnal paroxysmal dyspnoea. Her peripheral vessels were palpable. Her fundi were not abnormal. She complained of numbness of the legs which were stiff and heavy. No knee or ankle jerks were obtained but pin-prick appeared normally discernible.

She had been a diabetic for 4 years. At home she had 16 units of insulin and a diet but in hospital her fasting blood sugar was 220 and she required 25 units Z.P.I. for control. There was no family history of diabetes.

Post Mortem. Urinary system. The right kidney weighed 240 gms. The left 160. Both showed a little granularity but otherwise appeared normal.

Microscopically. There is considerable hyalinisation of the afferent arterioles but little other change.

Cardiovascular system. The right auricle was greatly distended, the left collapsed. The heart weighed

410 gms. chiefly due to hypertrophy of the left ventricle. The valves were healthy and competent. There was considerable myocardial fibrosis, especially in the region of the left coronary vessels. Both coronary vessels showed wellmarked atheroma, which was extreme in the left circumflex branch. In the area of this vessel on the posterior wall of the left ventricle, there were some small pericardial haemorrhages, suggestive of a recent infarct. The aorta showed some patches of calcification in its thoracic part, and moderate atheroma throughout, but this was not by any means outstanding. The abdominal vessels splenic, hepatic and duodenal showed well-marked atheroma.

CASES OF PYELONEPHRITIC GROUP.

Case 19. 8703.

An obese man of 80. He was admitted for gangrene of the left foot from which he ultimately succumbed. He had albuminuria 1+ and was febrile from no discernible cause. There was no oedema. A catheter specimen of urine showed no pus but on culture grew *Bacillus Morgani* and *Bacillus Proteus*. A suprapubic drainage was established a week after his admission because of retention. His blood urea after this was 62 mgs.%. A further specimen showed

no pus but was still positive on culture. He continued to be febrile, and this was not considered to be due to his gangrene which was dry. His blood pressure was 165/75. He showed no cardiac enlargement. He had no raised J.V.P. and no history of breathlessness. His right fundus was clear. His left fundus showed a few white patches but no haemorrhages. He had neither subjective nor objective signs of peripheral neuritis. His fasting sugar was 184 mgs.%. He had 15 sol. insulin night and morning during his stay and was not easily controlled.

Previous History. His previous history was considered to have shown a mild diabetes for 5 years. There had been an increase in frequency before admission, but no other renal history. There was no family history of diabetes.

Post Mortem. Urinary System. Left kidney weighed 235 gms. The surface was smooth and somewhat pale. There were several scars and numerous small abscesses as well as several dark irregular patches. On section no clear line could be made out between cortex and medulla. Several calyces were dilated and contained white pusy-looking fluid. Pelvis and ureter were inflamed and a little dilated. The right kidney was 210 gms. It was darker in colour and showed similar appearance to the left but to a lesser degree. The bladder was contracted and thick-walled. The mucous membrane was acutely inflamed and polypoid masses projected from the surface. It contained pus

and foul smelling urine.

Microscopically. The appearance are those of pyelonephritis.

Cardiovascular System. The heart weighed 395 gms. and was soft and somewhat flabby. There was a good deal of extrapericardial fat. The myocardium appeared healthy. The coronary arteries showed some atheroma but were widely patent. The aorta was not unduly atheromatous. The right femoral and posterior tibial showed pipe-stem thickening with encircling rings of the Monkeburg type. The lumen gradually narrowed from above down and the plantars were almost completely occluded.

Case 20. 15941.

A man of 18 of normal build. He was admitted with pulmonary tuberculosis and signs of spinal compression which ultimately proved to be tuberculous spinal meningitis and accounted for his death. He had acute retention of urine for which he had been previously catheterised, and which ultimately required suprapubic drainage. His urine showed a trace of albumen on admission which gradually developed to +++. He showed ++++ of pus and some red blood cells. Culture grew a Coliform Bacillus and Staph. Albus. He had no oedema. He was febrile most of the time but his tuberculous lesion was also active. There were no signs of hypertension or other vascular changes. His Hb. was 106%.

He had a cord compression at D.12 and no other signs of nervous involvement.

Previous History. He had no previous history of urinary trouble. He had been diabetic for 2 years of a severe type for which he got 30 Z.P.I. and 24 soluble and dieting but was still not controlled. It was very difficult to control during his stay in hospital.

There was no family history of diabetes.

Post Mortem. Urinary system. The kidneys were large and swollen. The capsule stripped easily leaving a sub-capsular surface which was slightly granular and speckled with numerous tiny abscesses. The cut surface showed numerous abscesses in the cortex. There was a slight increase in pelvic fat and moderate inflammation of the pelves. The ureters were normal. The bladder showed an acute pyogenic cystitis.

Microscopically. There are scattered cortical and medullary abscesses rich in clumps of coliform organisms.

Cardiovascular system. The heart weighed 380 gms. There was moderate left ventricular hypertrophy and dilatation. The muscle was pale and flabby and showed extensive fibrosis at the apex. The coronary arteries showed severe atheroma with practical occlusion of the lumen wide-spread in all branches. The aorta and branches showed moderate atheroma only.

Case 22. 76066.

A woman of 39 who had been obese at the beginning of her diabetes. She was admitted with neoplasm of the cervix from which she finally died. Her urine showed varying amounts of albumen sometimes none, sometimes trace, occasionally ++. She had no oedema. The diabetes was difficult to control. Her blood urea was 28 mgs% and her urea clearance test 58% of normal. An intravenous pyelogram showed right hydronephrosis and hydroureter. Her blood pressure was 105/75. Her haemoglobin was 76%. There was no cardiac enlargement clinically or on X-ray. She had a history of breathlessness on effort for about a year. There was no change in her eye grounds. There was no evidence of peripheral neuritis. She had intermittent spikes of temperature throughout her stay.

Previous history. She had received radium therapy 2 years previously at another hospital. There was no history of renal disease though she had nocturnal frequency since the radium. She had been diabetic for 5 years of a severe type, requiring 40/30 soluble Insulin and diet. There was no family history of diabetes.

Post Mortem. Urinary system. Both kidneys weighed 220 gms. Both ureters were injected with formol saline and the kidneys fixed for 2 days. The right kidney capsule stripped easily leaving a smooth surface with prominent stellate veins and numerous

fine cortical abscesses. The cut surface showed a dilated pelvis and calyces. Some papillae were definitely flattened. The pelvis wall was thickened and white. There was wasting of the sinus renalis fat. The cortex was riddled with numerous small abscesses some of which were confluent. There was surprisingly little atrophy of the medulla. The cortical pattern was good. The left kidney showed a similar sub-capsular appearance to the right, and numerous small cortical abscesses. The pelvis and calyces were dilated but most if not all of this may have been due to the fact that, in contrast to the right, the left kidney had been injected by formalin under pressure. The pelvis was thin and transparent. The right ureter was dilated and obstructed at the level of the pelvic brim by pelvic growth.

Microscopically. The right kidney shows extensive suppurative pyelonephritis with abscess formation. A few tubules in the cortex are enormously distended with cast material and the papillae appear excavated and concave instead of convex but hydronephrotic atrophy is hardly yet apparent. The left kidney shows a suppurative pyelonephritis.

Cardiovascular system. The heart weighed 220 gms. The muscle was pale and flabby. The coronary vessels were healthy and the aorta and branches fairly free of atheroma.

APPENDIX "B"

CLINICAL CASES of KIMMELSTIEL WILSON SYNDROME.

Series No.	No. of case	P.M. No.	
23	7690714	4511	M.W.
24	100263	4791	E.A.
25	71200		B.E.
26	55446		J.D.
27	24182		J.P.
28	94613		I.M.
29	21538		B.B.
30	102242		E.D.
31	90991		E.G.

CLINICAL CASES of ARTERIOSCLEROTIC GROUP.

Series No.	No. of case	
32	94212	M.B.
33	99107	A.D.
34	94814	W.A.
35	96720	F.P.
36	95512	W.T.

CLINICAL CASE OF CHRONIC GLOMERULONEPHRITIS

Series No.	No. of case	
37	92075	M.M.

SUMMARY of Clinical Cases with relevant signs,
symptoms and pathological findings.

CASES OF KIMMELSTEIL WILSON GROUP.

Case 23. 7690714.

A woman aged 68. She was 19 stone at the age of 46 but was now 8 st. 12 lbs.

She first came under observation one year before her death when her complaint was loss of vision, complete in the right eye and dyspnoea on exertion. She had had swelling of the ankles for the past two years and polyuria. She had two acute bouts of diarrhoea alternating with constipation.

On examination she was found to have glycosuria and the diabetes was confirmed by G.T.C. Her right eye showed intense iritis and marked corneal injection. There were new blood vessels on the iris. Both eyes had lens opacities.

At that time her B.P. was 120/65. Apex beat normal. She had oedema of both ankles, and occasional albuminuria.

A urea clearance test showed 81.4% of normal.

She was finally discharged without insulin to be kept on diet under observation.

She was re-admitted one year later because of general deterioration and to investigate the albuminuria now gross +++. She had had nocturnal paroxysmal dyspnoea for three months. She was now virtually blind and could only see light. She was now

hypertensive 182/118. Her J.V.P. was +2. Her liver was palpable 2fb's and she had oedema half way up her tibiae. There were basal creps. She had bilateral cataracts obscuring the view of the fundi. She complained of aching pains in the legs and numbness of both feet. Her calves were exquisitely tender and her abdominal and ankle jerks were missing

Her blood total protein was 4.4 gms.%.

Albumen 2.3. Glob. 2.1. Ratio 1.1.

Cholestrol 250 mgs. Blood urea 52 mg.%.

A diagnosis of Kimmelsteil Wilson syndrome was made on the clinical picture. She died very suddenly before further studies could be made of her renal function. P.M. confirmed the presence of gross intercapillary glomerulosclerosis.

POST MORTEM. Urinary system. Bladder and ureters were normal. Right kidney weighed 190 gms. - the left 180 gms. The appearances in each case were identical. The capsule stripped easily leaving a finely granular surface. The cortico-medullary junction was prominent and the cortex appeared yellower than usual.

Microscopically. Both kidneys showed gross abnormalities. The majority of the glomeruli have thickened basement membranes and show varying degrees of intercapillary glomerulosclerosis of the "nodular" type. The arterioles showed pronounced hyalisation, and the larger arteries splitting and reduplication of the elastica. There was also patchy

infiltration of the interstitial tissue by lymphocytes in the ischaemic area.

Cardiovascular system. The heart weighed 320 gms., with LV hypertrophy. The right auricle was dilated and the tricuspid orifice admitted the tips of four fingers. The left auricle was normal in size and the mitral valve slightly stenosed admitting only one finger. The mitral cusps were contracted and calcified.

The coronary vessels showed a minimal atheroma and had wide luninae. The aorta was moderately atheromatous. The cerebral vessels were normal.

Case 24. 100263.

An obese, cyanotic woman of 76.

She was seen for the first time with gangrene of the right foot and succumbed after operation. There was pitting oedema of both ankles, and of the affected leg below the knee.

Her urine was found to contain sugar, acetone and albumen ++ Blood Urea 53 mgs%.

A glucose tolerance test confirmed the diabetes of which there was no history. Fasting sugar was 240 mgs%. Her B/P was 270/150. The apex beat was in the 5th space 5 ins. from the midline. Her liver was enlarged. There were some basal crepitations. Occular fundi were not seen well owing to opacities but were thought to show some nipping.

She had no vibration sense below T 12 and superficial sensation in the lower limbs was impaired. The ankle jerks were absent.

She became incontinent of urine and febrile after operation, and in spite of penicillin and insulin did not progress and died of what appeared to be a myocardial infarction.

POST MORTEM. Urinary System. The right kidney weighed 210 gms. and was enlarged and flabby. The capsule was slightly adherent leaving a finely granular surface. The cortex was pale. The corticomedullary junction was not well preserved. Some congestion of the pelvis and some haemorrhages were present.

The left kidney weighed 150 gms. and was small and hard. The capsule stripped with some difficulty leaving a coarser granularity than that on the right side. On section, the pattern was not well preserved but small white patches were present especially in the cortex. The pelvis was slightly dilated, showed marked congestion, was haemorrhagic and contained much gravel extending into the major calyces. The bladder showed marked haemorrhagic purulent cystitis and gravel.

Microscopically. Both kidneys show, in addition to an acute pyelonephritis, an advanced state of intercapillary glomerulosclerosis. Nearly every glomerulus is affected. There are occasional "caps" of hyaline material on the Bowman's capsule, and

there is advanced arteriolosclerosis as well as ischaemic change.

Cardiovascular system. The heart weighed 360 gms.

There was a large amount of pericardial fat.

Valves normal. Aortic ring slightly calcified.

The left ventricle showed a small old area of fibrosis on the anterior wall. The coronary vessels were normal except for some narrowing of the descending branch of the left coronary. There was no occlusion of any of the coronary vessels. The aorta showed marked atheroma. The pulmonary artery contained post mortem clots extending into the subdivisions of the smaller vessels.

Case 25. 71200.

An obese woman of 72.

She was discovered to be diabetic $3\frac{1}{2}$ years ago. She was treated by diet only. She was admitted $2\frac{1}{2}$ years ago with pain in the legs, shooting in character, and unsteadiness of gait. She had no vibration sense in the legs and her ankle jerks were missing. Her blood pressure was 116/74 and she had cataracts in both eyes. There was a persistent trace of albumen in the urine. She was again admitted to hospital $1\frac{1}{2}$ years ago with a perforating ulcer of the foot. She admitted that she did not stick very closely to her diet. Her vision had by then deteriorated to such an extent that she could only read

with a strong magnifying lense. She had "pins and needles" in her hands; and had loss of sensation in her legs. She had no position sense in her toe joints and both ankle and knee jerks were absent even on reinforcement. Her blood pressure was 180/110, but she then had no complaints of dyspnoea. Haemorrhage and exudates could be seen in one eye, but the other was completely obscured. There was 1+ albumen in the urine. A diagnosis of Kimmelstiel Wilson syndrome was made.

She was admitted again 6 months ago as her condition seemed to be deteriorating. She now had a blood pressure of 250/150 and pitting oedema of both ankles. Her urine showed ++ albumen and some pus cells, which were cleared by chemo-therapy. She was still suffering from peripheral neuropathy and her vision had deteriorated to perception of light. Her total protein was 6.5 gms % albumen 3.5 gms %, globulin 3 gms %, ratio 1.2. Her cholestrol was 222 mgs % and Urea 26 mgs %. She was again admitted for investigation 3 months ago when her general condition seemed much the same, but she had again a urinary infection. When this infection was cleared 3+++ albumen remained. Her renal function was then estimated and gave the following results :

Essential Renal Plasma Flow 355 ML/min
Glomerular Filtration Rate 100 ML/min
Filtration Fraction .28
Tubular maximum glucose reabsorptive capacity 286

in mg/min

Threshold 286 mgs %

Since then, at her request, the cataract in her right eye was removed, but this was followed in 3 weeks by vitreous haemorrhages. She is now dyspnoeic even with the little exertion of which she is capable.

Case 26. 55446.

A woman of 61.

She came under observation 3 years ago when she had been diabetic for 3 years. Her complaint was pains in the legs. She was taking Z.P.I. 40 units and soluble insulin 20 units each morning, and had been admitted to another hospital for stabilisation one year ago. Her glucose tolerance curve (fasting and $\frac{1}{2}$ hourly) was 298, 472, 540, 524, 512. She had an adenomatous goitre which had been present for 25 years. Her blood pressure was 140/90. She had bilateral cataracts, no knee or ankle jerks, and had parathesias and limb pains. There was oedema of the ankles. She was readmitted 6 months later, suffering still from tingling pains and weakness in the legs, but on this occasion being also dyspnoeic, and her blood pressure was 168/100. Her urine showed a trace of albumen. The following year her cataracts were removed successfully. She was treated with thiouracil in view of the fact that her

goitre was considered overactive, but she did not tolerate it and it was discontinued.

She was admitted again one year ago, because her signs of hyperthyroidism had again increased. She had had an attack of hypertensive failure, and her blood pressure was 260/110. Thyroidectomy was done under local and convalescence was uneventful. Her urine now showed 1+ or 2++ albumen. Her insulin requirements were lessened to P.Z.I. 16 units, soluble insulin 8 units on which she seemed on good control. She continues to be dyspnoeic on effort, and to have albumen 2++. Her total proteins are 6.7 gms % with 3.7 gms % albumen, 3 gms % globulin. Her blood urea is 67 mgs % and plasma cholestrol 224 mgs %. Her renal function, after suitable rest in bed, was :

Essential renal plasma Flow 266 ML/min

Glomerular Filtration Rate 81 ML/min

Filtration Fraction .30

Tubular maximum glucose reabsorption capacity 286 mg/min

Her blood pressure remains 210/120.

Case 27. 24182.

A woman of 76.

She was first seen 7 years ago. She had then been diabetic for four years, treated by diet and 12 units of insulin but was admitted because she

still had glycosuria and pruritis. Her blood pressure was 150/75. There was no albuminuria, no oedema of the ankles, and all her jerks were present.

One year later she was readmitted with "sciatica". She had tenderness in the right leg and thigh, but all jerks were present and there was no sensory loss. Her diabetes required 36 units soluble insulin twice a day for control. Her blood pressure was now 190/90 but there were no symptoms. She had a trace of albumen.

After discharge she continued to have pains in both legs and tingling and "pins and needles" in the arms.

Two years later she was admitted in hypoglycaemic coma which was soon corrected. She now had oedema of both ankles, worse at night. Her fundi showed diabetic retinopathy, her blood pressure was 190/80, and her urine showed a constant trace of albumen.

She was admitted 6 months ago for restabilisation. She had pronounced diabetic retinopathy. Her blood pressure was 190/100. She had 1.8 gms albumen /24 hour urine. Her total protein was 6.2 gms %, albumen 3.5 gms %, globulin 2.7 gms %. Cholestrol 217 mgs %, blood urea 49 mgs %.
Essential Renal Plasma Flow 264 Ml/min
Glomerular Filtration Rate 76 Ml/min
Filtration Fraction .29

Tubular maximum glucose reabsorptive capacity

152 mg/min

Threshold 200 mgs %

Her ankle jerks were now absent and she was dyspnoeic on moderate exertion.

Since then she has remained in remarkable health, living comfortably within her limits.

Case 28. 94613.

A woman aged 62, obese.

She was admitted for the first time 7 months ago. She was in congestive cardiac failure with gross oedema of the legs, which had been present for 3 weeks. She had had numbness of the legs for the previous 6 months but no other previous ill-health. Her J.V.P. was +6, blood pressure 218/112. Liver enlarged 2 finger-breadths. Crepitations at both bases. Gross pitting oedema to the thighs. She had 29 gms of albumen /24 hours urine, which fell to 8.2 gms when the heart failure was controlled by digitalis. There was gross glucosuria and her Glucose Tolerance Curve (fasting and $\frac{1}{2}$ hourly) was 259, 266, 450, 323, 304. Her diabetes eventually required P.Z.I. 32 units and soluble insulin 12 units to control. Her cholestrol at first 466 mgs % dropped to 296 mgs %. Her total proteins were 6.6 gms % but fell to 5.6 gms %. Electrophonetic analysis of the blood proteins

showed albumen 80.5%, Beta globulin 17.5%, Gamma globulin 13.0%. The urine contained albumen 80.5%, globulin 19.5 gms.%. The urinary globulin appeared to consist of two components, the slower moving component predominating. After many weeks she improved to be able to move about the ward without dyspnoea and her kidney function was then estimated.

Essential Renal Plasma Flow 373 Ml/min.

Glomerular Filtration Rate 49.1 Ml/min.

Filtration fraction .13.

Tubular Maximum Glucose reabsorption capacity 106 mg/min.

Threshold 215 mgs.%.

She was readmitted again 2 months later, again in congestive failure. She then had dyspnoea on the least exertion, and had had two attacks of nocturnal paroxysmal dyspnoea. Her JVP was +5 cms. Blood pressure 205/110. Crepitations at both bases. She had pitting oedema to both groins. Her plasma proteins were 5.6 gs. total, albumen globulin ratio being 1.2. Her urinary albumen was still 3+++.

Her retinopathy had increased and her vision was steadily deteriorating. She made an excellent recovery on digitalis and salt free diet and was discharged after six weeks, able to move about gently without dyspnoea, and has remained, living within her limits, since.

Case 29. 21535.

A woman of 68.

She first came under observation because of bilateral cataracts, which led to the discovery of her diabetes six years ago. In spite of her cataracts the fundi were visualised and showed such a degree of diabetic retinopathy that operation was not advised.

Three years after this, she showed albuminuria and at that time the suggestion was made that she might show an early Kimmelstiel Wilson syndrome. Since then she has been reasonably well, apart from a mild urinary infection which responded well to chemo-therapy. Six months ago she was admitted for stabilisation, as her renal threshold appeared clinically to be high. Investigations showed that her blood pressure was 180/110. She had tenderness of the calves and some impairment of sensation to the knees. There was occasional swelling of the ankles. She was not then dyspnoeic on effort but has become so since and has occasional raised J.V.P. and crepitations at bases. Her renal studies showed her

Essential Renal Plasma Flow 312 ML/min

Glomerular Filtration Rate 73.1 ML/min

Filtration Fraction .24

Tubular maximum glucose reabsorption capacity 237 mg/min

Threshold 323 mgs %.

She had 2++ albumen in the urine, and her urine contained doubly refractile bodies.

She had not previously had insulin but is now having P.Z.I. 10 units. Her total proteins are 6.6 gms %, albumen 3.3 gms %, globulin 3.3 gms %, Plasma cholestrol 271 mgs %. Blood urea 50 mgs %.

She remains in reasonable health living quietly within her limits.

Case 30. 102242.

A woman of 66.

She was referred from another hospital because of weakness and parasthesia in both hands. She had had deteriorating vision for 3 years because of bilateral cataracts. Her urine was loaded with sugar and her fasting blood sugar was 380 mgs %. She was hypertensive, blood pressure 190/95 and dyspnoeic on effort. She had pitting oedema of variable extent of the ankles. Her urine showed 3 gms albumen /24 hours. Her plasma protein was 6.0 gms % with albumen 4.1 gms %, and globulin 1.9 gms %, cholestrol 235 mgs %

Urea 29 mgs %

Essential Renal Plasma Flow 360 Ml/min

Glomerular Filtration Rate 62 Ml/min

Tubular Maximum Glucose reabsorption capacity 144.8 mg/min

Threshold 240 mgs %.

Her urea clearance was 68.9 Ml/min.

She was put on diet and insulin and is progressing slowly on return to the original hospital.

Case 31. 90991.

A man of 64.

He was first admitted to hospital 2 years ago when he was diagnosed as pseudo-tabes, with persistent oedema of the ankles of unknown origin. At that time there was an occasional 1+ albuminuria, and he had a diabetic retinopathy, by no hypertension his blood pressure being 130/90. He confessed that his occupation of cook gave him free access to foods not on his diet and his diabetes, in spite of 20 units Z.P.I., and 20 units soluble insulin, was not stable. He has since proved to be careless of his diabetes, being admitted several times either in precoma or hypoglycaemia. His pseudo-tabes improved to the extent that he lost his unsteadiness and his knee jerks returned. He remained however rather weak and having some pains in the legs.

Six months later, on readmission in hypoglycaemia occasioned by taking his insulin but no food, his blood pressure was 155/100 on recovery, and his urine showed 2++ albuminuria.

He was readmitted six months ago in precoma, having taken no insulin for 2 days. On recovery his J.V.P. was +2, blood pressure 160/80 and some

basal crepitations were present. There was gross oedema of the ankles. His retina showed a very marked diabetic retinopathy and his vision was now too bad for reading. After many weeks of treatment he was able to get about without dyspnoea but his ankles remained swollen. His blood proteins, having been 5.8 mgs % before were now 6.4 mgs % and cholestrol from 415 mgs % fell to 313 mgs %. His urine albumen remained about 5 gm /24 hours. His renal studies done six weeks after his precoma state, showed

Essential Renal Plasma Flow 195 Ml/min

Glomerular Filtration Rate 63.7 Ml/min

Filtration Fraction .32

Tubular Maximum Glucose reabsorption capacity 127 mg/min

Threshold 204 mgs %.

He was found a light job in the hospital kitchens, but proved quite unamenable to discipline, and unreliable even under constant supervision, besides being physically incapable of any exertion. His diabetes was most difficult to stabilise and he was finally discharged on P.Z.I. 40 units, soluble insulin 12 units each morning.

CLINICAL CASES of Arteriosclerotic Group.

Case 32. 94212.

A thin senile woman of 68, looking much more than her years. She was known to be diabetic for 10 years but had no insulin. She was admitted 7 months ago for gangrene of the right foot, which was amputated. The left foot had a very impaired circulation, dorsalis pedis very palpable, but remained cold but free from gangrene. Her blood pressure was 180/90, her vessels clearly palpable. She was disorientated at night which was thought to be due to cerebral arteriosclerosis. She had a history of two strokes but there was no clinical residuum. Her urine contained a constant proteinuria, varying from a trace to 2++. There were no doubly refractile bodies. She had no subjective or objective signs of peripheral neuropathy. Her fundus was seen to show arteriosclerotic changes, with nipping of the veins and tortuosity of the arteries. Her operation was accomplished without incident. Her renal dynamics, done before the operation when her general condition was good, showed :

Essential Renal Plasma Flow 108 Ml/min

Glomerular Filtration Rate 24 Ml/min

Filtration Fraction .22

Tubular Maximum Glucose reabsorption capacity 33 mg/min

Threshold 137 mgs %.

She returned home reasonably well, and attended the diabetic clinic for two further occasions. No change was noted in her condition. Four months after the operation she was admitted to another hospital where she died from cerebral thrombosis. No post mortem was obtained.

Case 33. 99107.

A thin, senile woman of 82. She had been diabetic for 12 years, but had been treated with diet only. She had been dyspnoeic on effort for 2 years and was suffering from occasional paroxysmal nocturnal dyspnoea. Her blood pressure was 280/110 and she had left ventricular preponderance on her Electrocardiograph. All her arterial vessels were tortuous and hard and she had a marked "locomotor brachialis". She had neither subjective nor objective evidence of peripheral neuropathy. Her eyesight was good and there was no retinopathy. Her blood urea was 49 mg %. She was alleged to have had a stroke but no residua were observed. There was a constant 1+ albuminuria. When she had recovered from her mild degree of failure, after one month in hospital she still had 1+ albuminuria. There were no doubly refractile bodies. Her renal dynamics then were :

Essential Renal Plasma Flow 125 Ml/min

Glomerular Filtration Rate 41 Ml/min

Filtration Fraction .33

Tubular Maximum Glucose reabsorption capacity 62
mg/min

Threshold 150 mgs %

Two months after discharge she died at home of
cerebral thrombosis.

Case 34. 94814.

A thin man of 73.

He was found to be diabetic when he presented
with gangrene of one toe. He was admitted in the
first place to the medical wards, 7 months ago.
Neither dorsalis pedis was palpable. His blood
pressure was 170/100. All jerks were present and
there were no subjective signs of peripheral neuro-
pathy. There was some macular degeneration in both
eyes but no retinopathy of diabetic or hypertensive
type. He had no oedema and was not breathless on
exertion. Oscillography showed the circulation in
his right leg to be so defective that it was consider-
ed advisable to amputate the leg. His renal
dynamics, done after prolonged rest and prior to
operation, were:

Essential Renal Plasma Flow 381 Ml/min

Glomerular Filtration Rate 91 Ml/min

Filtration Fraction .24

Tubular Maximum Glucose reabsorption capacity 122
mg/min

Threshold 131 mgs %

There were no doubly refractile bodies in the urine.

He made an uninterrupted recovery and is now attending regularly, the other foot giving rise to some anxiety.

Case 35. 96720.

A thin woman of 71.

She had been a known diabetic for 15 years. She had cataracts removed from her eyes 5 years previously and had been on 10 units P.Z.I. since. She had remarkably arteriosclerotic vessels. Her retina showed pronounced tortuosity of the arterioles and "nipping" of the veins, but nothing characteristic of diabetic neuropathy. Her blood pressure was 250/120. She had advanced osteoarthritis and Heberden's nodes on both hands. She was admitted 5 months ago for investigation. Her cholestrol was 193 mgs %, her total proteins 6.7 gm %, albumen 3.9 mgs %, Globulin 2.8 mgs %, Blood urea 32 mgs. There was a constant 1+ of albumen but no doubly refractile bodies. She had neither subjective nor objective symptoms of peripheral neuropathy, and no oedema. Her renal studies showed:

Essential Renal Plasma Flow 341.5 Ml/min

Glomerular Filtration rate 44 Ml/min

Filtration Fraction .13 mg/min

Tubular Maximum Glucose reabsorption capacity 62 mg/min

Threshold 139 mgs %

She accidentally fractured her humerus and attends regularly without much change being apparent in her general condition.

Case 36. 95512.

A frail man of 82.

He had been diabetic for 12 years, treated by diet only. He was perfectly well until four months before admission to hospital. He then developed angina and breathlessness on effort, with some oedema of the ankles and was admitted 7 months ago for this reason. He quickly lost the oedema and seemed very well although E.C.G. showed an anterior myocardial infarct. He made a good recovery. He had thickened and palpable arteries and marked locomotor brachialis. He had no retinopathy and no peripheral neuropathy. His urine showed a trace to 1+ albumen, even after clinical recovery. His renal studies done at that time showed :

Essential Renal Plasma Flow 160 Ml/min

Glomerular Filtration Rate 38 Ml/min

Filtration Fraction .23

Tubular maximum glucose reabsorption capacity

60 mg/min

Threshold 154 mgs.

He is understood to have died at home some 2 months after leaving, of a further myocardial infarction.

CLINICAL CASE OF CHRONIC GLOMERULONEPHRITIS.

Case 37. 97252.

A woman of 38, who had been diabetic for 26 years always requiring insulin as well as diet. Six years ago she had an attack of acute nephritis, with oedema of face, eyes and legs, haematuria and hypertension (blood pressure 190/120). Within a few days her blood pressure fell again to 125/90 and she made an apparently good recovery, except that she continued to have albuminuria which has since remained. Since then she has had pyuria on five occasions which has cleared by chemo-therapy. She only became hypertensive in the last year, when she exhibited a severe retinopathy with vitreous haemorrhages in one eye. Her ankle jerks were doubtful though she had no neuropathy. Her urine contains 2++ albumen, but no doubly refractile bodies. Her total protein is 6.8 gms with 3.4 gms albumen and 3.4 gms globulin. Her urine concentrating power is now very reduced and her blood urea runs about 90 mgs %. Her haemoglobin is 68%.

She continues to be remarkably fit, being in very easy circumstances and most co-operative in her treatment.